RAPID NETWORK META-ANALYSIS USING DATA FROM THE U.S. FOOD AND DRUG ADMINISTRATION APPROVAL PACKAGES AND CLINICALTRIALS.GOV – A CASE STUDY ON FIRST-LINE MEDICATIONS FOR GLAUCOMA

by

Lin Wang

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Abstract

Background

Network meta-analysis (NMA) extends pairwise meta-analysis by synthesizing both direct evidence within trials and indirect evidence across trials. NMA can address a broader research question than pairwise meta-analysis by comparing all interventions for a given condition in a single analysis. However, identifying, collecting, appraising, and synthesizing all relevant evidence is resource-intensive and time-consuming. Bibliographic databases such as PubMed, Embase and The Cochrane Register of Controlled Trials (CENTRAL) are almost always searched to identify trial reports. For regulated products (e.g., pharmaceuticals and biologics), approval packages available from the U.S. Food and Drug Administration (FDA) website (Drugs@FDA) contain information about trials that supported the marketing approval. ClinicalTrials.gov is another data source that can be tapped to identify trial reports.

Objective

To test a rapid NMA approach using Drugs@FDA and ClinicalTrials.gov to identify trials of drug interventions; to compare the usefulness of these two data sources to that of bibliographic databases; and to assess how results might be affected by using different data sources.

Methods

Building upon a recent NMA and available data sets, we searched ClinicalTrials.gov for randomized controlled trials on first-line medications for glaucoma. Two individuals

independently selected trials and extracted data. When a trial was identified in multiple sources, we compared trial reports from different data sources. We fit random effects NMA models to analyze trial reports from different data sources for intraocular pressure (IOP) at 3 months, the outcome of interest. We compared the findings from these analyses.

Results

We identified 115 trial reports from bibliographic databases, 28 from Drugs@FDA, and 27 from ClincalTrials.gov. These 170 trial reports described 139 unique trials including 29,158 participants. Only 78% (121/139) of the unique trials provided sufficient data for NMAs. When a trial was associated with multiple reports from different sources, information provided were inconsistent across the three sources in PICOT (patient, intervention, comparator, outcome, and time point), statistical methods, and results. ClinicalTrials.gov provided less trial information compared to Drugs@FDA and bibliographic databases. The effect estimates generally agreed when different sources of data were used for NMA, although the precision varied.

Conclusions

A rapid NMA approach using Drugs@FDA to identify trials of drug interventions is feasible. In our case example, NMA based on trial reports from Drugs@FDA alone provided reasonably precise estimates of relative effects. Reporting of trial design and results can be improved in both the drug approval packages and on ClinicalTrials.gov.

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1 Introduction

Systematic review is comprehensive but slow in production.

A systematic review uses systematic methods to identify, collect, appraise, and synthesize the body of evidence to address a clearly defined research question.[1] Conclusions drawn from systematic review can inform healthcare practice, public policy, insurance coverage, and future research.[2] Meta-analysis, an optional component of systematic review, uses statistical methods to combine results from individual studies.[3]

Although being regarded as a cornerstone of evidence-based practice, systematic reviews are not produced fast enough to meet decision-making needs.[4-8] It takes between 6 months to 2 years to conduct a systematic review, with the median time from final search to publication being 15 months.[5,9,10] A large proportion of time is devoted to identifying relevant studies from searching multiple data sources, which are not available from a single library or website.[11] Collecting all relevant evidence requires a comprehensive search of multiple databases and sources to identify eligible studies.[1,12-14] Public data sources for systematic reviews include journal articles, conference abstracts, trial registrations, regulatory information, whereas clinical study reports (CSRs) and individual patient data are less accessible to the public.[11]

Systematic reviewers search a median number of four databases, screen 5,000 or more citations, typically, 10% of which are considered relevant and are reviewed in full text, and 1% are ultimately included in a systematic review.[15-17] With the fast-evolving

technology and emerging public health problems, there are increasing demands for access to up-to-date research evidence. The considerable time and resource requirements for systematic review production may not be conducive for the decision-making paradigm.

Compared to traditional pairwise meta-analysis, network meta-analysis (NMA) facilitates multiple treatment comparisons but it usually requires a broader evidence base.

As a quantitative component of systematic reviews, pairwise meta-analysis addresses the question of the relative effects of two interventions by combining (as a weighted average) the results of multiple studies that have assessed the two interventions.[18,19] When properly conducted, pair-wise meta-analysis can improve the precision of estimates, explore heterogeneity and inconsistencies among individual studies, and inform future research questions.[1]

However, there are usually more than two interventions available for a given condition. Doctors and patients are sometimes offered a bewildering number of treatment options. Taking first-line medical treatment for open angle glaucoma as an example, patients can choose from more than ten different types of eye drops approved by the U.S. Food and Drug Administration (FDA) from four different classes.[20-22] Traditional pairwise meta-analysis cannot address the question "which treatment works best?" In some cases, different pairwise meta-analyses produced contradictory results, precluding a coherent picture of the comparative effectiveness of all treatments.[23-25]

The ever-increasing treatment options in clinical practice create urgent needs for sophisticated evidence synthesis methods that go beyond pairwise comparisons. NMA, an extension of pairwise meta-analysis, can address a broader research question than pairwise meta-analysis by comparing *all* interventions for a given condition in a single analysis.[26] As indicated by its name, NMA aims to build a network where nodes represent interventions while the edges represent direct comparisons between two interventions.[26-28] NMA facilitates indirect comparisons of interventions that have not been studied in a head-to-head manner.[29] If two interventions A and B have one intermediate comparator C, A and B can be compared indirectly providing indirect evidence. In cases where studies that directly compared treatments A and B also exist, combining direct and indirect evidence (as a weighted average) can increase the precision in effect estimates.[29-31] NMAs can therefore accomplish the task of "all-way" comparisons.

Two types of findings are produced by NMA: relative effect estimates of any two interventions in the network and ranking probabilities of all interventions.[32,33] Conclusions on the comparative effectiveness of all interventions in a network can be drawn based on both the estimates of relative effects and ranking probabilities.

Given that NMA is highly informative for decision-making by providing relative effects of multiple interventions, it has been used increasingly in the assessment of health technologies, especially pharmacological interventions.[33-35] The improved capability gained in NMA is not without cost. Compared to pairwise meta-analysis, NMA requires a broader scope of search to include all relevant interventions and studies.[35]

Rapid approach with limited search is appealing for systematic review.

Rapid reviews, defined as reviews that use methods to accelerate traditional systematic review process, have been introduced to provide timely information for decision making in recent years.[9,35] When Hartling and colleagues surveyed users of systematic reviews (guideline developers, healthcare providers, research funders, and health insurers), they found that limiting the literature search by database, journal, year is among the most acceptable trade-offs to increase efficiency.[36] Rapid reviews are deemed necessary when timeliness is crucial, and especially when a traditional systematic review is unavailable. For example, Medicare faces increasing pressure to conduct health technology assessments within less than 2 months.[37] More recently, Canadian Agency for Drugs and Technologies in Health offers "Rapid Response Service" to healthcare providers and other decision makers that are tailored to their urgent/time-sensitive inquiries.[38,39] Cochrane Rapid Review Methods Group was established in 2015 to develop rapid review methodology in the hope that reviews are produced quickly without sacrificing scientific rigor.[40]

Shortcuts in literature search may pose a threat to validity of the review findings, a concern that can only be addressed by empirical research.[9,36,41] Some researchers have found that searching data sources in addition to MEDLINE generated small incremental gain.[14,42] Furthermore, almost all the empirical research has been conducted in the context of systematic reviews using pairwise meta-analysis but not NMA. We describe known issues around data sources for pairwise meta-analysis below and will outline knowledge gaps for NMA.

Regulatory information and trial registration complements published literatures for systematic reviews.

Regulatory information and trial registration can provide data unavailable from published literature about trials included in systematic reviews.[12,43] For drugs approved by FDA, the approval packages available from Drugs@FDA (https://www.fda.gov/Drugs/InformationOnDrugs/ucm135821.htm) contain summaries of trials submitted to the agency for marketing approval. They are available on the agency's website for drugs approved since 1997; for drugs approved before 1997, information must be requested through a freedom of information request (https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm).[44] Similar regulatory documents are available at Health Canada Products Database and European Medicines Agency's European Public Assessment Reports.[45,46]

ClinicalTrials.gov, run by the United States National Library of Medicine (NLM) of the National Institutes of Health (NIH), is one of the largest clinical trials registries worldwide. ClinicalTrials.gov was established in 2000 in response to the trial registration requirement of the 1997 Food and Drug Administration Modernization Act (FDAMA 1997) (and therefore trials conducted before 2000 may not be identifiable from ClinicalTrials.gov).[47,48] It was expanded in 2008 to include a database for registering summary results under 2007 Food and Drug Administration Amendment Act (FDAAA 2007). [49,50] The 2016 "final rule" issued by Department of Health and Human Services and complementary "final policy" issued by NIH further expanded regulatory mandates for trial registration and results submission. The final rule and final policy require that

clinical trials (except phase I and early device trials) of FDA-regulated drugs, biologics, and devices, and clinical trials funded in whole or in part by the NIH be registered and have summary results information posted as of January 18, 2017.[51-54] As of April 03, 2018, ClinicalTrials.gov has included registrations for more than 270,000 studies from 203 countries and summary results for more than 30,000 studies.[55] There are also other trial registries available, such as WHO International Clinical Trials Registry Platform (ICTRP)[56] and EU Clinical Trial Register (EU CTR).[57]

For pairwise meta-analysis, the value of data from FDA approval packages and ClinicalTrials.gov has been demonstrated in many empirical studies.[58-62] Above all, FDA approval packages and ClinicalTrials.gov serve as valuable sources for identifying unpublished trials.[60,63] Previous studies also have examined completeness and accuracy of information presented in published literature with information provided in the FDA approval packages or ClinicalTrials.gov, as a way to examine selective reporting. In general, data reported in published literature showed a greater treatment effect overall than data presented in non-published data sources.[43,58,64,65] Selective reporting impacts the results and inferences in systematic reviews and meta-analyses.[65,66]

Knowledge gaps for NMA

In the context of NMA, we have identified two empirical studies that examined the usefulness of data from FDA approval packages and ClinicalTrials.gov. Trinquart and colleagues examined the impact of reporting bias in NMA using 74 trials identified from FDA approval packages and their 51 matching publications.[67] Trials identified from the

FDA approval packages were considered as the reference and internally "valid". After conducting a series of NMAs, the authors found that when trial results were partially or inaccurately reported in journal articles, the effect sizes would be overestimated, and the relative rankings of drugs would differ when using these two different data sources. [67] This study builds the case that FDA approval packages are an important source for identifying trial reports for drug interventions, and perhaps provide more valid data than their matching publications.

Cameron and colleagues conducted a rapid NMA on the effectiveness of antithrombotic medications for atrial fibrillation, where the authors analyzed data derived solely from ClinicalTrials.gov and compared findings with those based on data retrieved from *The Cochrane Library*, MEDINE, and Embase, the traditional approach.[68] Compared to the traditional approach, the rapid approach identified 6/12 trial reports (78,444/82,396 participants) covering 8/11 available interventions; trials missed were those published before the launch of ClinialTrials.gov results database in 2008.[68] The authors argued that clinical conclusions based on the rapid approach were similar to those based on traditional approach where all trials were identified, however, the rapid approach only took a few weeks, a fraction of time and resources compared to the traditional approach.[68]

These two examples suggest that NMA may be less sensitive to partial retrieval of all available data and that the choice of data source matters. Either omitting or focusing on ClinicalTrials.gov and/or FDA approval packages alone for NMA will save time and resources.

In this study, we aim to address the following questions: Is it worth looking for trial data from Drugs@FDA and ClinicalTrials.gov for NMAs of drug interventions? How different would the results be by using different data sources (i.e., Drugs@FDA or ClinicalTrials.gov compared to traditional bibliographic databases) in NMAs? To expedite the production of NMA, is it sufficient to only include trial data from Drugs@FDA or ClinialTrials.gov for NMA of drug interventions?

Objectives

To test a rapid NMA approach using Drugs@FDA and ClinicalTrials.gov to identify trials of drug interventions; to compare the usefulness of these two data sources to that of bibliographic databases; and to assess how results might be affected by using different data sources.

2 Methods

We built upon a recent NMA and available dataset on the comparative effectiveness of first-line medications for open angle glaucoma conducted by our group.[22] **Table 1** summarizes the status of dataset that was made available for this thesis research. In brief, the underlying NMA has already identified and extracted data from trials published in the bibliographic databases, including the Cochrane Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, and Embase. The search was run in March 2014 without any date or language restriction. A search of the Drugs@FDA was completed in April 2014. ClinicalTrials.gov was searched in the current study in December 2016.

Eligibility Criteria

We used the same eligibility criteria as the previous NMA.[22] Trials were eligible for our NMA if they meet all of the following criteria: (1) they were randomized controlled trials (RCT) with parallel design; (2) 60% or more participants had a diagnosis of primary open angle glaucoma or ocular hypertension; (3) they evaluated first-line topical medications in reducing intraocular pressure (IOP) or progression of visual field damage; (4) they compared a single active treatment with no treatment/placebo or another single active treatment.[22]

Trials were excluded if: (1) they enrolled less than 10 participants in each group; (2) they evaluated combination medications (generally prescribed after treatment failure of single

first-line medication); or (3) participants were followed for an outcome for less than 28 days after randomization.[22]

The primary outcome for the systematic review and NMA is mean IOP at 3 months in millimeters of mercury (mmHg). If more than one IOP measures were available, we used the following priority order in data extraction: mean diurnal IOP (the average of IOP values measured during daytime), 24-hour mean IOP, peak IOP value, morning IOP, and trough IOP value. When the 3-month IOP measure was not available, we used the IOP measured at a follow-up time point closest to 3 months.

Identifying trials from ClinicalTrials.gov

Working in collaboration with a trained information specialist (Lori Rosman), we searched ClinicalTrials.gov using a combination of generic drug names, brand names, and synonyms in December 2016 (search strategy available in **Appendix 1**). We downloaded search results from ClinicalTrials.gov as comma-separated values and imported them into a database for de-duplication and assessment of eligibility.

Trial selection

Two individuals independently assessed the trial registration records identified by the searches for potential eligibility. Discrepancies were resolved through discussion with a third person.

Data extraction and risk of bias assessment

Two individuals independently extracted data from each included trial. We extracted data items on study design, PICOT (patient population, intervention, comparison, outcome, and time points), risk of bias, and quantitative results for IOP using existing electronic forms developed by our group in the Systematic Review Data Repository (http://srdr.ahrq.gov).[69,70]

We used the Cochrane Risk of Bias Tool to assess the risk of bias in the following domains: randomization sequence generation, allocation concealment, masking of participants, and masking of IOP assessors.[1] We also documented the funding source(s) for each trial. Discrepancies were resolved through discussion with a third person.

Mapping trials identified from different data sources

In this thesis, we will use bibliographic database, Drugs@FDA, and ClinicalTrials.gov to describe data sources; and will use journal articles, approval packages, and trial registrations to refer to the types of records available from each data source.

A trial may be identifiable from more than one data source. For example, a trial published in a journal article (and identified from searching bibliographic databases) may also be identifiable from Drugs@FDA or Clinicaltrials.gov. We matched trials identified from Drugs@FDA and ClinicalTrials.gov to trials identified from bibliographic databases. We also matched trials between Drugs@FDA and ClinicalTrials.gov. We used trial publication link and trial registration number on Clinicaltrials.gov, the sponsor, the intervention and comparator, the description of trial design and results for matching.

When a trial was identified from more than one data source, we compared the completeness and consistency of information including trial design, the intervention and comparator, baseline characteristics, outcomes (including the primary and secondary outcomes of the trial), and results.

Qualitative synthesis

We evaluated the characteristics of included trials by data sources to examine the usefulness of the three data sources. We compared characteristics such as the year of trials and the sample size, the regions where the participants were recruited, the eligibility criteria, the follow-up time, and the type of analysis used.

Quantitative synthesis

In all analyses, we combined different concentrations of the same medication. Our effect estimate is the mean difference in IOP at 3 months for each pair of treatment comparison. In RCTs, the baseline mean IOP is expected to be balanced among treatment groups. Therefore, difference in mean change from baseline between two groups estimates the same underlying relative effect as mean difference between two groups using only the follow-up values.[1] We thus combined mean reduction in IOP at 3 months with mean IOP at 3 months in our analysis.

We analyzed five networks of trials: (1) all unique trials identified from three data sources; (2) trials identified from bibliographic databases alone; (3) trials identified from Drugs@FDA alone; (4) trials identified from ClinicalTrials.gov alone; (5) trials identified

from bibliographic databases but not found on Drugs@FDA or ClinicalTrials.gov. For all-unique trial network, when data were available from more than one source, we chose data source using the following order of priority: Drugs@FDA, bibliographic databases, ClinicalTrials.gov. For other trial networks, we used data from the corresponding data source.

For each network, we first conducted pairwise meta-analyses for every direct comparison using a DerSimonian and Laird random-effects model,[71] implemented in STATA package 'metan'.[72-74] We used two assumptions for heterogeneity to test the robustness of results to different assumptions: comparison-specific heterogeneity and common heterogeneity across all comparisons.[71]

We then fit random-effects NMA models following the approach by Chaimani and White, executed using the STATA 'stataNMA' package.[74-76] We first assumed consistency and a common heterogeneity across all comparisons in the network. When evidence of statistical inconsistency was detected, we also fit an inconsistency model and compared the model fit.

We estimated the probabilities for each intervention to achieve each possible rank among all interventions (i.e. being the most effective, the second most effective, all the way till the least effective).[32,74] We plotted a cumulative ranking curve for each intervention. The SUCRA (surface under the cumulative ranking curve) value represents the probability an intervention is among the top X of all interventions compared.[32,74]

Evaluating NMA assumption

We first evaluated the assumption of transitivity qualitatively. Transitivity indicates the indirect estimates are valid estimates of the unobserved direct comparisons through transitive comparators.[29,31] Transitivity is violated when: the anchor treatment differs systematically between trials; the choice of the comparison is associated with relative effectiveness; treatments included have different indications.[31] We considered the interventions analyzed in the networks to have the same indication because we only included first-line glaucoma medications.

We then evaluated the assumption of consistency statistically (i.e., the agreement of direct and indirect estimates) using three approaches: loop-specific approach, modeling inconsistency approach, and side-split approach[76-81], executed using the STATA 'stataNMA' package.[74-76]

When evidence of statistical inconsistency was found, we examined the accuracy of data extraction and the trial characteristics that may influence the effect estimates, including the outcome specification, the funding source, the type of analysis, and other characteristics. We conducted sensitivity analysis by removing trials that were suspected to have introduced statistical inconsistency.[29]

We used STATA 14 (StataCorp LP, College Station, TX) for all pairwise meta-analyses and NMAs.

3 Results

3.1 Identification of trials

We identified 115 trial reports from searching bibliographic databases (**Appendix 2**), 28 from Drugs@FDA, and 27 from ClinicalTrials.gov (**Figure 1**). These 170 reports described 139 unique trials. **Figure 2.1** and **Table 2** show the extent of overlap of trials among these three data sources.

Only 78% (132/170) trial reports (or 121/139 unique trials) provided sufficient data for pairwise meta-analysis and NMA of IOP at 3 months, the outcome on which these drugs were approved (**Figure 2.2**). This is particularly concerning for pivotal trials identified from Drugs@FDA (57%, 16/28). Data needed for meta-analysis were least complete for trials identified from ClinicalTrials.gov (33%, 9/27).

3.2 Characteristics of included trials

Because the goal is to compare and assess the usefulness of different data sources for providing data for a systematic review and NMA, we describe the characteristics of included trials below by data source (and thus 170 trial reports in total instead of 139 unique trials).

Years and size of the trials

The characteristics of 170 included trial reports are described in **Table 3**. Trials identified from bibliographic databases were published between 1983 to 2016 (median=2002).

Trials identified from the Drugs@FDA were submitted to FDA for regulatory review between 1997 and 2012 (median=2000). Trials identified from ClinicalTrials.gov were completed (i.e., completed final data collection for primary outcome) between 1993 and 2014 (median=2009). There were no ongoing or terminated trials relevant to our analysis.

A total of 29,158 participants were studied in these 139 unique trials (170 trial reports) with a sample size ranging from 17 to 1,159. The median sample size of trials from bibliographic databases, Drugs@FDA and ClinicalTrials.gov was 111 (Interquartile range (IQR), 50-260), 350 (IQR,186-573), and 267 (IQR, 163-586) respectively. Although only a small number of trials were identified from the Drugs@FDA and ClinicalTrials.gov, trials identified from these two data sources are larger in size: trials from each source contributed about one third of all participants (11,417 and 10,145 respectively). However, data from one quarter (25%, 7,167/29,158) of participants from these two sources were not published.

Regions in which participants were recruited

Most trials were multicenter trials. Trials identified from bibliographic databases reported recruiting participants from broader geographic regions than trials identified from the Drugs@FDA and ClinicalTrials.gov; the latter two reported recruiting participants primarily from North America and Europe.

Specifically, 73/115 trials identified from bibliographic databases reported region(s) from which participants were recruited. Of them, 63% (46/73) reported North America, 26%

(19/73) reported Europe, 21% (15/73) reported Asia, 4% (3/73) reported Latin America, 5% (4/73) reported Oceania, and 1% (1/73) reported Africa.

Twenty-six of 28 trials identified from the Drugs@FDA reported region(s) from which participants were recruited. Of them, 88% (23/28) reported North America, 15% (4/28) reported Europe, 4% (1/28)reported Asia, 4% (1/28) reported Latin America, 4% (1/28) reported Oceania, and 0% (0/28) reported Africa.

Twenty-four of 27 trials identified from ClinicalTrials.gov reported region(s) from which participants were recruited. Of them, 79% (19/24) reported North America, 21% (5/24) reported Europe, 0% (0/24) reported Asia, 0% (0/24) reported Latin America, 0% (0/24) reported Oceania, and 0% (0/24) reported Africa.

Eligibility criteria

Ocular hypotensive medication was allowed at enrollment in most trials, yet a washout period was not always required in these trials. Specifically, 82% (94/115) trials identified from bibliographic databases reported allowing enrollment of participants who were taking ocular hypotensive medication on enrollment, and 83% (78/94) of which reported requiring a washout period before randomization. Eight nine percent (25/28) of trials identified from the Drugs@FDA reported allowing enrollment of participants who were taking ocular hypotensive medication on enrollment, and 88% (22/25) of which reported requiring a washout period before randomization. Fifty nine percent (16/27) of trials identified from ClinicalTrials.gov reported allowing enrollment of participants who were

taking ocular hypotensive medication on enrollment, and 63% (10/26) of which reported requiring a washout period before randomization.

Follow-up time

The median length of follow-up was 3 months. The reported duration of follow-up ranged from 1-73 months (median=3 months) for trials identified from bibliographic databases, 1-15 months (median=3 months) for trials identified from the Drugs@FDA, and 1-12 months (median=3 months) for trials identified from ClinicalTrials.gov.

Type of analysis

The reporting of type of analysis was poor in trials identified from bibliographic databases and ClinicalTrials.gov - only 55% (63/115) and 59% (16/27) respectively provided information, as compared to 89% (25/28) trials identified from the Drugs@FDA. When such information was available, intention-to-treat analysis was the most commonly reported analysis. Intention-to-treat analysis was reported in 65% (41/63) trials identified from bibliographic databases, 84% (21/25) trials identified from the Drugs@FDA, and 16% (13/81) trials identified from ClinicalTrials.gov.

Qualitative analysis of transitivity assumption

We did not find systematic difference of the anchor treatment between trials in terms of drug concentration, dosage, or duration of treatment, nor did we find evidence suggesting that the choice of the comparison is associated with relative effectiveness. Timolol, the most commonly used comparison intervention among the included trials, was compared with all other drugs directly in at least one trial.

3.3 Risk of bias assessment (Table 4, Figure 3)

Assessing the risk of bias is challenging for trials identified from Drugs@FDA and ClinicalTrials.gov because details describing the design and conduct were generally not available from these two sources.

Most trials did not report random sequence generation and allocation concealment (unclear risk of bias). For trials identified from ClinicalTrials.gov, the percentage of non-reporting was 100% (27/27) and 100 % (27/27) for each domain, respectively. For trials identified from Drugs@FDA, the percentage of non-reporting was 93% (26/28) and 93% (26/28) for each domain, respectively. For trials identified from bibliographic databases, the percentage of non-reporting was lower: 54% (62/115) and 65% (75/115) for each domain, respectively.

When masking was reported, the study participants and IOP assessors were not masked (high risk of bias) in some trials: 21% (24/115) and 10% (11/115) of trials identified from bibliographic databases, respectively; 30% (8/27) and 4% (1/27) of trials identified from ClinicalTrials.gov. For trials identified from Drugs@FDA, the percentages were lower: 7% (2/28) and 7% (2/28), respectively. In addition, many trials (>70%) reported single, double or triple masking, but did not specify the role of person who was masked.

Most trials were funded by pharmaceutical industry, especially for trials identified from Drugs@FDA (100%, 28/28) and ClinicalTrials.gov (93%, 25/27). For trials identified

from bibliographic databases, the percentage reported funding from pharmaceutical industry was lower (56%, 65/115).

3.4 Comparison of reporting of key characteristics of trials

When reports of the same trial were identified from more than one source, we compared the information on PICOT (patient population, intervention, comparison, primary and secondary outcomes, and time points), statistical methods, baseline characteristics, and results. A list of all characteristics we compared is available in **Tables 5-8**. We highlight noticeable differences in the text below.

3.4.1 Bibliographic databases vs Drugs@FDA vs ClinicalTrials.gov (**Table 5**)

Only four trials (reported in three journal articles) allowed this three-way comparison. We found that journal articles identified from bibliographic databases and approval packages identified from Drugs@FDA generally provided more information in terms of participants, trial design, statistical methods, and results than trial registrations identified from ClinicalTrials.gov.

Trial registrations tended to provide information concerning only the primary outcome of the trial and adverse events, while journal articles and approval packages also provided information on secondary outcomes.

Sample size calculation was reported only in journal articles. Participant flow diagram was available from both journal articles and trial registrations, but not from approval

packages. Quantitative results of our primary outcome (IOP at 3 months) generally agreed among three sources.

3.4.2 Bibliographic databases vs Drugs@FDA (**Table 6**)

The comparison of 10 trials identified from both bibliographic databases and Drugs@FDA suggested that journal articles generally provided more information regarding trial design and statistical methods, while approval packages provided more information regarding secondary outcomes of the trials such as visual field, vertical cup/disc ratio, central visual acuity.

The two sources sometimes provided inconsistent eligibility criteria. Some eligibility criteria were described in only one source but not both. For example, in one trial (Table 6 No.5), "intraocular surgery within the past 12 months" was listed in exclusion criteria in the journal article [Sall K 2000] but not in the corresponding approval package [CDER NDA20816].

The description of primary outcome and primary analysis of some trials differed between the two sources. For example, for one trial (Table 6 No.6), the journal article reported mean change in diurnal IOP at 6 months as primary outcome while the approval package reported mean IOP averaged over four timepoints (weeks 2, 6 and months 3, 6) as primary outcomes. For two trials, per-protocol analysis was reported in the journal articles as the primary analysis while intention-to-treat was reported in the approval packages as the primary analysis. The results therefore differed.

The quantitative results of IOP at 3 months differed substantively for one trial: the journal article reported that the mean IOP difference between bimatoprost group and timolol group was -1.89 mmHg (95% confidence interval [CI]: -2.70, -1.09) (Table 6 No.4), whereas the approval package reported a result of -2.07 mmHg (95% CI: -2.92, -1.23). Moreover, for three trials reported in journal articles, outcomes reported in the result section were not prespecified in the methods section of the articles, raising concern of selective reporting.

3.4.3 Bibliographic databases vs ClinicalTrials.gov (**Table 7**)

The comparison for 12 trials showed that half of the trial registrations identified from ClinicalTrials.gov had no results at all. For three trials with results posted on ClinicalTrials.gov, IOP data were not reported although IOP was among the outcomes according to the corresponding journal articles.

Journal articles generally provided more information with regards to trial design, statistical methods, and results than trial registrations. However, trial registrations always provided patients flow diagram, which was not the case for journal articles.

The two sources sometimes provided inconsistent eligibility criteria. Some eligibility criteria were described in only one source but not both. Length of follow-up differed for two trials. The number of study groups disagreed for two trials. The specification of primary outcome and the quantitative results of IOP generally agreed.

Type of analysis was described in three trial registrations with much less information than what was available from the corresponding journal articles. Methods of handling missing IOP data were not described in any trial registrations.

3.4.4 Drugs@FDA vs ClinicalTrials.gov (**Table 8**)

Only one trial was identified from both sources. In this case, trial registration provided more information than the approval package. The choice of primary outcome differed, with the approval package reported mean IOP at a follow-up time point, while the trial registration reported mean IOP change from baseline.

Summary

Taken all together, among the three data sources, journal articles provided the most information about trials for systematic review, while trial registration provided the least. Approval packages provided more information on secondary outcomes of the trial than the other two sources. Trial registrations always provided a patient flow diagram. Eligibility criteria disagreed in some cases. The primary outcome and primary analysis sometimes disagreed. The quantitative results of IOP at 3 months generally agreed.

Table 9 summarizes the strengths and limitations of each data source for systematic review.

3.5 Comparison of quantitative results

For the convenience of description of quantitative results, in this section we refer to trials identified from bibliographic databases as "published trials", trial identified from Drugs@FDA as "FDA trials", trials identified from ClinicalTrials.gov as "ClincalTrials.gov trials", trials identified from bibliographic databases but not found on Drugs@FDA or ClinicalTrials.gov as "published trials not found on FDA or ClincalTrials.gov".

3.5.1 Pairwise meta-analyses

Only 121 of the 139 unique trials provided sufficient data for meta-analysis. The 121 unique trials from all three sources generated 39 direct comparisons. Half of the direct comparisons were informed by very few trials: 12 (31%) direct comparisons were based on one trial and eight (21%) were based on two trials. For each direct comparison, a median number of two trials (interquartile range 1-5.5) were included. There were 110 (91%) two-arm trials, 10 (8%) three-arm trials, and one (1%) four-arm trial. Timolol, the most popular comparator, was studied in 71 (59%) trials.

Table 10.1 shows the summary estimates of mean difference in IOP at 3 months derived from pairwise meta-analyses of all unique trials. When compared directly with placebo, eight drugs (brimonidine, betaxolol, levobunolol, timolol, levobetaxolol, brinzolamide, dorzolamide, and bimatoprost) resulted in statistically significant lower IOP; while there was no evidence suggesting unoprostone lowered IOP more than placebo. The estimated mean reduction in IOP (vs placebo) ranged from 1.33 to 7.51mmHg. When compared directly with timolol, three drugs (bimatoprost, latanoprost, and travoprost) showed better

efficacy in IOP reduction, while five other drugs (levobetaxolol, brinzolamide, dorzolamide, tafluprost, and unoprostone) did not. The estimated mean difference in IOP (vs timolol) ranged from -2.09 to 1.43. The results assuming a common heterogeneity are comparable to the results assuming a comparison-specific heterogeneity.

Table 10.2-10.5 and **Figure 4** present the pairwise effect estimates (relative to placebo or timolol) derived from different networks of trials (published trials, FDA trials, ClinicalTrials.gov trials, published trials not found on FDA or ClinicalTrials.gov). The effect estimates of these drugs relative to placebo or timolol generally agreed among three sources although precision varied.

3.5.2 NMAs

The number of interventions included differed among different networks: 15 for the all-unique trial network (121 trials, 20981 participants), 14 for the published trial network (107 trials, 17,343 participants), 10 for the FDA trial network (16 trials, 5,250 participants), and 6 for the ClinicalTrials.gov trial network (nine trials, 2,296 participants) (**Figure 5.1 through 5.4**). The all-unique trial network and published trial network are well-connected polygons; the FDA trial network is star-shaped (interventions were compared to a common comparator but not to one another); the ClinicalTrials.gov trial network is a poorly connected. For FDA trial network and ClinicalTrials.gov trial network, more than 50% of direct comparisons were based on one trial. (**Table 11**)

NMA of all-unique trial network

Table 12.1 shows the effect estimates generated from NMA that combined direct and indirect evidence of all unique trials. In this analysis, we assumed consistency and a common heterogeneity across all comparisons in the network. All 14 drugs were more efficacious than placebo in reducing IOP at 3 months. The mean reductions (95% CIs) in IOP (mmHg) at 3 months, from the most efficacious one to the least, are: bimatoprost 5.60 (4.90, 6.29), travoprost 4.90 (4.19, 5.61), tafluprost 4.77 (3.53, 6.01), latanoprost 4.72 (4.09, 5.34), levobunolol 4.54 (3.80, 5.29), timolol 3.73 (3.17, 4.28), carteolol 3.46 (2.41, 4.51), brimonidine 3.00 (2.28, 3.71), brinzolamide 2.91 (2.11, 3.71), levobetaxolol 2.53 (1.42, 3.65), dorzolamide 2.33 (1.64, 3.01), betaxolol 2.27 (1.60, 2.95), apraclonidine 2.00 (0.28, 3.72), unoprostone 1.86 (1.06, 2.66). Bimatoprost led to a statistically significant lower IOP at 3 months than any other drugs except tafluprost, where the two confidence intervals overlapped.

The probabilities for each drug (plus placebo) to achieve each one of the 15 possible ranks are present in **Figure 6.1**, arranged from the least efficacious drug to the most efficacious drug. The ranking probabilities are consistent with the treatment effect estimates. For example, bimatoprost has a 90.5% probability of being ranked as the most efficacious intervention, while placebo has a 98.9% probability of being ranked as the least efficacious.

The cumulative rankings for each drug are plotted in **Figure 7.1**. For each of the 15 interventions (14 drugs plus placebo) included in the all unique trial network, the X axis presented the possible ranks (in this case, it ranges from 1 to 15), and the curve plotted

the cumulative probability that a drug is among the top x treatment. If a drug has a 100% probability to be the best, the curve would rise and plateaued at the first rank, and the SUCRA (surface under the cumulative ranking curve) value would be one. On the opposite, if a drug has a 100% probability of being the worst, the curve would level out and not rise till the 15th rank, the SUCRA value would then be zero. The SUCRA values and mean ranks are consistent with the treatment effect estimates (**Table 13**). For example, bimatoprost has the highest SUCRA value of 99.3 and the highest mean rank of 1.1, while placebo has the lowest SUCRA value of 0.1 and the lowest mean rank of 15. Of note, relative ranking should not be over-interpreted as small differences in effect estimates may not be clinically important.

NMAs of other trial networks

The results of NMAs derived from different sources (published trials, FDA trials, ClinicalTrials.gov trials, published trials not found on FDA or ClinicalTrials.gov) are presented in **Table 12.2-12.5, Figure 6.2-6.5, Figure 7.2-7.5.** The effect estimates of comparative effectiveness of these drugs generally agreed among three sources although precision varied.

Figure 8 presents the treatment effect estimates relative to timolol based on NMAs of different networks. The effect estimates generally agreed among different sources although precision varied. Of note, for bimatoprost, travoprost, and brinzolamide, where NMAs of published trials and the FDA trials found statistically significant differences from timolol, NMA of ClinicalTrials.gov trials failed to detect significant differences.

This was likely due to small number of trials (and thus low power) included in the ClinicalTrials.gov network.

Table 13 displayed the SUCRA values and mean ranks generated by NMAs. The relative ranking generally agreed among different sources. Compared to the rankings of 15 interventions generated by NMA of all unique trials, NMA of FDA trials produced the same relative rankings for the 10 available interventions. NMA of published trials produced the same relative rankings for the 14 available interventions with a position switch between dorzolamide and betaxolol. Noticebly, NMA of ClinicalTrials.gov trials produced different relative rankings for the six available interventions with two position switches - between bimatoprost and travoprost, and between brimonidine and brinzolamide, respectively.

For both pairwise and network meta-analysis, the results from published trials that were not found on FDA or ClinicalTrials.gov are similar to those from all published trials, but with reduced precision.

3.5.3 Evaluation of inconsistency

We assessed inconsistency between direct and indirect evidence using three different approaches (**Appendix 3**). Inconsistency assessment was not applicable to ClinicalTrials.gov trial network because there was no closed loop, i.e., no direct vs indirect evidence. Inconsistency assessment was also not applicable to FDA trial network

because although there were closed loops, they are from multi-arm trials, i.e., no direct vs indirect evidence.

Loop-specific approach

We used loop-specific approach to estimate an inconsistency factor (IF) for each closed loop in the all-unique trial network. We assumed a common heterogeneity for all comparisons within each loop but different heterogeneity across loops. We found 36 triangular loops and 13 quadratic loops. Evidence of statistical inconsistency was detected in three (8%) triangular loops.

In order to explore potential reasons for statistical inconsistency, we examined characteristics of trials involved in these tree triangular loops. We identified three trials that were outliers with larger effect size than the other trials examining the same comparisons. All three trials were published trials, two of which were published before 1990. IOP was measured at 9 months post treatment for one trial. The funding source was unclear for two trials, and was pharmaceutical industry for the third trial. All three trials did not specify the type of analysis used for primary outcome. The different time points of outcome measurement and the unclear type of analysis may have resulted in larger effect size in the three trials and hence statistical inconsistency in the three triangular loops.

We detected evidence of statistical inconsistency in the same three (9%) triangular loops in the published trial network. We addressed the inconsistency by conducting a sensitivity analysis removing these three trials (see 5.4).

Modeling inconsistency

We applied a design-by-treatment interaction inconsistency model to check for overall inconsistency in the all-unique trial network. We found inconsistency at the overall level with a P value of 0.0038. When the inconsistency model and consistency model were compared using both Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for model fit, inconsistency model did not improve the model fit. We also detected evidence of overall inconsistency in published trial networks. Similarly, inconsistency models did not improve the model fit. We therefore chose consistency model over inconsistency model as our final model.

Side-split approach (node-split approach)

We used side-specific approach to estimate local inconsistency in the all-unique trial network. Evidence of statistical inconsistency was found in two (5%) sides. These two sides (levobunolol vs placebo and timolol vs levobunolol) were from one of the three triangular loops where loop-specific inconsistency was detected (see 5.3.1). We found evidence of statistical inconsistency in the same two sides in the published trial network.

Summary

We detected evidence of statistical inconsistency in all-unique trial network and published trial network. We fit inconsistency models which did not improve the model fit. We explored the potential source of statistical inconsistency by qualitative analysis. We address the inconsistency by sensitivity analysis removing three susceptible outlier trials (see 5.4).

3.5.4 Sensitivity analysis

For sensitivity analysis, we re-analyzed the all-unique trial network after removing 3 trials that were outliers and that may have introduced heterogeneity and inconsistency. We did not conduct sensitivity analysis for other networks because of the small number of trials included in those networks. The effect estimates and ranking probabilities from the sensitivity analyses were consistent with our primary analyses (**Appendix 4**).

4 Discussion

In this study, we tested the feasibility of a "rapid" NMA approach, in which trials were identified from Drugs@FDA and ClinicalTrials.gov. We found that compared to using all unique trials identified from all three data sources (bibliographic databases, Drugs@FDA, and ClinicalTrials.gov), using trial from Drugs@FDA alone, we were able to generate reasonably precise effect estimates and the same relative rankings for available interventions. However, using trials from ClinicalTrials.gov alone, we were not able to generate precise effect estimates or consistent ranking.

Rapid approach with limited search is feasible for NMA

Our findings support that rapid approach with limited search is possible for NMA for drug interventions. The results of NMA may be more robust (less sensitive) to the change in the number of trials included. In our case, the FDA trial network contains fewer trials than all-unique trial network (16 vs 121). However, the effect estimates and the relative rankings produced by these two networks are consistent for the available interventions. There are two possible explanations for this. First, in the FDA trial network, drugs were indirectly compared through a common comparator timolol. The network is no longer a well-connected polygon but a radiant star. The star-shaped network raised less concern over the assumption of transitivity. Second, the potential bias might be mitigated through the common comparator.[74] That is, if industry sponsored trials were biased in favor of new drugs as compared to timolol, the indirect comparisons among multiple new drugs, which were connected through timolol, could be less biased.

Drug@FDA is a useful data source for rapid NMA

FDA approval packages have been used by previous studies as "gold standard" to examine selective reporting and its impact on meta-analysis including NMA.[64,67,82,83] Our study advances previous research by illustrating that Drugs@FDA is a valid data source for rapid NMA. Based on our findings, conducting a rapid NMA with trial data from FDA approval packages would be an efficient choice for decision-makers who need a quick snapshot of comparative effectiveness of approved drugs for a condition. Since these trials were conducted under FDA's jurisdiction, their protocols and analyses were reviewed by FDA. Compared to searching bibliographic databases, identifying trials from Drugs@FDA requires much less time and resource. The search itself is straightforward as only drug generic name is needed.

In addition, we found that approval packages from Drugs@FDA provided more detailed information with regards to secondary outcome and adverse events of trials than bibliographic databases and ClinicalTrials.gov. It has been shown that published trial reports of drug interventions may exaggerate benefit and downplay harms compared to internal reports and regulatory documents: outcomes were selectively reported; numbers of adverse events were understated; serious adverse events including deaths were omitted.[84-89] ClinicalTrials.gov only requires reporting of "serious adverse events and other adverse events that exceed a threshold of 5% within comparison group".[53] The addition of FDA approval packages to published data has revealed increased harm in meta-analyses.[82] Therefore, our findings are of interest to systematic reviewers as Drugs@FDA is a valuable source to tap into for research of regulated drugs.

However, one caveat of Drugs@FDA is that not all approval packages are readily available from Drugs@FDA and the information presented in the approval packages may be limited or incomplete for meta-analysis. As noted earlier, approval packages are available on the agency's website for drugs approved since 1997;[44] for drugs approved before 1997, information must be requested through a freedom of information request (https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm). In our study, we could not retrieve approval packages for levobunolol, apraclodine, and cartelol, which were approved by FDA in 1985, 1987, and 1988, respectively. Our requests for approval packages for these three drugs were not responded by FDA In addition, the precision measures for the primary outcome (i.e., IOP at 3 months) of these pivotal trials were not reported in 42% of trials, limiting the usefulness of approval packages for NMA.

It also should be noted that approval packages often are available only for the first indication approved and not for later indications (although one may request those documents, which are usually brief). They are only available for products regulated by FDA. Therefore, Drugs@FDA does not include "over-the-counter (OTC) products marketed without an application", "dietary supplements", "biological products regulated by Center for Biologics Evaluation and Research", or "drugs not approved by FDA".[90]

ClinicalTrials.gov, in its current form, may not be very useful for rapid NMA

We found ClinicalTrials.gov least useful for NMA. Among three data sources, ClinicalTrials.gov provided the least complete trial information, despite the purpose of its establishment--to provide health care professionals and researchers with easy-to-access

clinical study information.[91] Most trials completed before the initiation of the website in 2000 were not available. Trial results collected before the launch of the result database in 2008 were not available. In our case, 8/27 of the trial registrations identified from ClinicalTrials.gov had no results, of them, 7/8 were completed before 2008. Similarly, previous studies also have found that less than 50% ClinicalTrials.gov trial registrations had reported results.[66,68,92-94]

In addition, ClinicalTrials.gov only requires summary information about a trial protocol and results. Therefore, drug dose and regimen were not available in many trial registrations; sample size calculation and ways of handling missing data were not available; the results of secondary outcomes and adverse events of trials were incomplete compared to their corresponding trial reports from bibliographic databases and Drugs@FDA. Similar to the findings of our study, Zarin and colleagues found that 61% ClinicalTrials.gov registry records lacked specificity of outcome metric, 24% reported results for 90% or less of their participants.[95]

The search of ClinicalTrials.gov did identify 10 trials (4/10 with sufficient data for meta-analysis) that were neither published or described in FDA approval packages. These trials could have been useful for NMA, had the trial information been complete. Overall, the status quo of ClinicalTrials.gov limits its usefulness for NMA.

Can systematic reviews and NMAs be done more efficiently?

In an ideal world, all trials (and all reports and related information about trials) should be indexed in one place. Findings from trials should be presented in a standardized and structured format to facilitate systematic reviews. However, problems need to be overcome before systematic reviews and NMAs can be done more efficiently. At the current time, searching one data source cannot identify all relevant studies. Trial information provided by available data sources are far from complete. In addition, disagreements were found among different data sources in primary outcome, sample size, and estimates of both benefit and harm effects of drugs.[11,58-62,96]

In our study, disagreements were found around patient eligibility criteria, choice of primary outcome, and primary analysis. The goal of a clinical trial is to demonstrate the effectiveness and safety of interventions in a study population. With inconsistent eligibility criteria, it is difficult for health care professionals and researchers to interpret and apply the trial findings. The inconsistency in describing primary outcome and primary analysis is also problematic because results could be cherry-picked by trialists to better align with their hypotheses.

With regard to the presentation of information, journal articles and FDA approval packages typically are presented in PDF format and information needed for systematic reviews must be located and extracted manually. There is no cross-agency or cross-division standard format for preparing trial summaries that are included in the FDA approval packages (personal communication). In our study, we observed variations of how trials were described across approval packages. In contrast, ClinicalTrials.gov has

standardized and tabulated format for organizing data, which is easier for data extraction (although data are incomplete).

Areas for improvement

For regulatory agencies with an increasingly open attitude towards data sharing, our findings shall draw their attention to the scope and quality of trial information to share with the public. Bennett and colleagues[97] proposed that FDA should consider integrating components of the CONSORT (Consolidated Standards of Reporting Trials)[98] in its description of trials. Trial registration numbers should always be included in the FDA approval packages. In addition to approval packages, the recent FDA pilot program of sharing CSRs is also a promising step forward.[99]

CSRs contain unabridged and comprehensive descriptions of the clinical problem, design, conduct, and results of clinical trials, following a structure and content guidance prescribed by the International Conference on Harmonization.[100] CSRs can be particularly useful for identifying detailed information about harms (in addition to efficacy outcomes). Because the results are in the aggregate form, they are easy to analyze and sufficient for most systematic reviews. However, CSRs can be thousands of pages in length, which require more time to extract and analyze data than public sources.

For trial registries, our findings highlight the incompleteness of information registered. The minimal data elements required are insufficient for understanding the design and results of trials for the purpose of systematic reviews. The requirement of trial protocol

submission may mitigate this problem. In addition, links to publications should be kept up-to-date. In our experience, when trials were registered, not all trials reports were linked to the trial registration. In addition, when auxiliary studies were linked to the trial registrations, there was no easy way to find out whether the analyses in these studies were based on randomized comparisons.

Limitations and strengths

Our study used first-line glaucoma medication as a case study. We only examined regulatory data from Drugs@FDA and registration information from ClinicalTrials.gov. Therefore, our conclusions should not be overly-generalized. We recognized that we searched the three databases at different time point (March 2014 for bibliographic databases, April 2014 for Drugs@FDA, and December 2016 for ClinicalTrials.gov). However, only two of the 27 eligible trials we identified from ClincialTrials.gov were completed (i.e., completed final data collection for primary outcome) after April 2014. Excluding these two trials is unlikely to change our key findings and conclusions.

In terms of strengths, we validated a rapid approach for NMA by comparing it with a comprehensive approach which covers both published and unpublished evidence. We conducted a full range of comparisons of trial information in PICOT, statistical methods, and results. Our study enriched the empirical evidence supporting a rapid approach for NMA. Future research should test this approach in other clinical areas; in the assessment of long-term clinical outcomes, patient-centered outcomes, and adverse events; and in the

exploration of other data sources such as clinical study reports and individual patient data.

5 Conclusion

A rapid NMA approach using Drugs@FDA to identify trials of drug interventions is feasible. In our study, NMA based on trials from Drug@FDA alone provided reasonably precise estimates of relative effects. Reporting of trial design and results can be improved in both drug approval packages and on ClinicalTrials.gov.

6 Reference

1. Higgins JPT, Green S(editor). Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.
2. Evidence-based Practice Centers (EPC) program overview. Content last reviewed January 2018. (Accessed April 21, 2018, at http://www.ahrq.gov/research/findings/evidence-based-reports/overview/index.html.)
3. GLASS GV. Primary, secondary, and meta-Analysis of research. Educational Researcher 1976;5:3-8.
4. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Annals of Internal Medicine 2007;147:224-33.
5. Sampson M, Shojania KG, Garritty C, Horsley T, Ocampo M, Moher D. Systematic reviews can be produced and published faster. Journal of Clinical Epidemiology 2008;61:531-6.
6. Beller EM, Chen JK, Wang UL, Glasziou PP. Are systematic reviews up-to-date at the time of publication? Systematic Reviews 2013;2:36.
7. Tsafnat G, Glasziou P, Choong MK, Dunn A, Galgani F, Coiera E. Systematic review automation technologies. Systematic Reviews 2014;3:74.
8. Hartling L, Guise JM, Kato E, et al. AHRQ comparative effectiveness reviews. EPC Methods: An Exploration of Methods and Context for the Production of Rapid Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015.
9. Ganann R, Ciliska D, Thomas H. Expediting systematic reviews: methods and implications of rapid reviews. Implementation Science : IS 2010;5:56.
10. Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. Systematic Reviews 2012;1:10.
11. Mayo-Wilson E, Li T, Fusco N, Dickersin K. Practical guidance for using multiple data sources in systematic reviews and meta-analyses (with examples from the MUDS study). Research Synthesis Methods 2018;9:2-12.
12. AHRQ Methods for Effective Health Care. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
13. Institue of Medicine. Finding what works in health care: standards for systematic reviews. Washington, DC: The National Academies Press; 2011.
14. Halladay CW, Trikalinos TA, Schmid IT, Schmid CH, Dahabreh IJ. Using data sources beyond PubMed has a modest impact on the results of systematic reviews of therapeutic interventions. Journal of Clinical Epidemiology 2015;68:1076-84.
15. Wallace BC, Trikalinos TA, Lau J, Brodley C, Schmid CH. Semi-automated screening of biomedical citations for systematic reviews. BMC Bioinformatics 2010;11:55.
16. Rosman L TC, Li M, Li T, Saldanha I, Dickersin K. Teaching searching in an intensive systematic review course: "how many citations should I expect to review?". Cochrane Colloquium. Quebec, Canada2013.

17. Page MJ, Shamseer L, Altman DG, et al. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional Study. PLoS Medicine 2016;13:e1002028.
18. Chalmers I. The Cochrane collaboration: preparing, maintaining, and disseminating systematic reviews of the effects of health care. Annals of the New York Academy of Sciences 1993;703:156-63; discussion 63-5.
19. Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: when one study is just not enough. Clinical Journal of The American Society of Nephrology : CJASN 2008;3:253-60.
20. Boland MV, Ervin AM, Friedman D, et al. AHRQ comparative effectiveness reviews. Treatment for Glaucoma: Comparative Effectiveness. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
21. Boland MV, Ervin AM, Friedman DS, et al. Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. Annals of Internal Medicine 2013;158:271-9.
22. Li T, Lindsley K, Rouse B, et al. Comparative effectiveness of first-Line medications for primary open-angle glaucoma: A systematic review and network meta-analysis. Ophthalmology 2016;123:129-40.
23. Li T, Ervin AM, Scherer R, Jampel H, Dickersin K. Setting priorities for comparative effectiveness research: a case study using primary open-angle glaucoma. Ophthalmology 2010;117:1937-45.
24. Li T DK, Scherer RW. Re: Registering systematic reviews. Canadian Medical Association Journal 2010;182:13-4.
25. Li T, Vedula SS, Scherer R, Dickersin K. What comparative effectiveness research is needed? A framework for using guidelines and systematic reviews to identify evidence gaps and research priorities. Annals of Internal Medicine 2012;156:367-77.
26. Li T, Puhan MA, Vedula SS, Singh S, Dickersin K. Network meta-analysis-highly attractive but more methodological research is needed. BMC Medicine 2011;9:79.
27. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in Medicine 2004;23:3105-24.
28. Salanti G, Kavvoura FK, Ioannidis JP. Exploring the geometry of treatment networks. Annals of Internal Medicine 2008;148:544-53.
29. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC Medicine 2013;11:159.
30. Song F, Harvey I, Lilford R. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. Journal of Clinical Epidemiology 2008;61:455-63.
31. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Research Synthesis Methods 2012;3:80-97.
32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of Clinical Epidemiology 2011;64:163-71.
33. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. PloS One 2014;9:e99682.

34. Lee AW. Review of mixed treatment comparisons in published systematic reviews shows marked increase since 2009. Journal of Clinical Epidemiology 2014;67:138-43.
35. Tonin FS, Rotta I, Mendes AM, Pontarolo R. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. Pharmacy Practice 2017;15:943.
36. Hartling L, Guise JM, Hempel S, et al. Fit for purpose: perspectives on rapid reviews from end-user interviews. Systematic Reviews 2017;6:32.
37. Eisenberg JM, Zarin D. Health technology assessment in the United States. Past, present, and future. International Journal of Technology Assessment in Health Care 2002;18:192-8.
38. About the rapid response service. Canadian Agency for Drugs and Technologies in Health, 2018. (Accessed April 21, 2018, at https://www.cadth.ca/about-cadth/what-we-do/products-services/rapid-response-service.)
39. Khangura S, Polisena J, Clifford TJ, Farrah K, Kamel C. Rapid review: an emerging approach to evidence synthesis in health technology assessment. International Journal of Technology Assessment in Health Care 2014;30:20-7.
40. Cochrane methods rapid reviews. The Cochrane Collaboration, 2018. (Accessed April 21, 2018, at http://methods.cochrane.org/rapidreviews/welcome.)
41. Tsertsvadze A, Chen YF, Moher D, Sutcliffe P, McCarthy N. How to conduct systematic reviews more expeditiously? Systematic Reviews 2015;4:160.
42. Sampson M, Barrowman NJ, Moher D, et al. Should meta-analysts search Embase in addition to Medline? Journal of Clinical Epidemiology 2003;56:943-55.
43. Hopewell S, McDonald S, Clarke M, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. The Cochrane Database of Systematic Reviews 2007:Mr000010.
44. Turner EH. How to access and process FDA drug approval packages for use in research. BMJ (Clinical Research Ed) 2013;347:f5992.
45. European public assessment reports (EPAR). (Accessed April 18, 2018, at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125.)
46. Drug Product Database online query. (Accessed April 21, 2018, at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp.)
47. Food and Drug Administration Modernization Act of 1997. 1997.
48. Robert Mehnert KGC. Press release: National Institutes of Health launches "ClinicalTrials.gov". National Library of Medicine; 2000.
49. Tse T WR. ClinicalTrials.gov to include basic results data. NLM Tech Bull;2008 Sep-Oct:e15.
50. Food and Drug Administration Amendments Act of 2007. 2007.
51. Clinical trials registration and results information submission. Final Rule. Federal Register 2016;81:64981-5157.
52. Hudson KL, Lauer MS, Collins FS. Toward a new era of trust and transparency in clinical trials. JAMA 2016;316:1353-4.
53. Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - The Final Rule. The New England Journal of Medicine 2016;375:1998-2004.
54. NIH Policy on the dissemination of NIH-funded clinical trial information. In: Health NIo, ed.2016:64922-8 (7 pages).

55. Trends, charts, and maps. U.S. National Library of Medicine. (Accessed April 21, 2018, at https://clinicaltrials.gov/ct2/resources/trends.)
56. International Clinical Trials Registry Platform (ICTRP). World Health Organization. (Accessed April 21, 2018, 2018, at http://www.who.int/ictrp/network/en/.)
57. EU Clinical Trials Register. European Medicines Agency. (Accessed April 21, 2018, 2018, at https://www.clinicaltrialsregister.eu/ctr-search/search.)
58. Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. JAMA 2009;302:977-84.
59. Dwan K, Altman DG, Cresswell L, Blundell M, Gamble CL, Williamson PR. Comparison of protocols and registry entries to published reports for randomised controlled trials. The Cochrane Database of Systematic Reviews 2011:Mr000031.
60. Scherer RW, Huynh L, Ervin AM, Taylor J, Dickersin K. ClinicalTrials.gov registration can supplement information in abstracts for systematic reviews: a comparison study. BMC Medical Research Methodology 2013;13:79.
61. Becker JE, Krumholz HM, Ben-Josef G, Ross JS. Reporting of results in ClinicalTrials.gov and high-impact journals. JAMA 2014;311:1063-5.
62. Hartung DM, Zarin DA, Guise JM, McDonagh M, Paynter R, Helfand M. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. Annals of Internal Medicine 2014;160:477-83.
63. MacLean CH, Morton SC, Ofman JJ, Roth EA, Shekelle PG. How useful are unpublished data from the Food and Drug Administration in meta-analysis? Journal of Clinical Epidemiology 2003;56:44-51.
64. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. The New England Journal of Medicine 2008;358:252-60.
65. Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings: an updated review of related biases. Health Technology Assessment (Winchester, England) 2010;14:iii, ix-xi, 1-193.
66. Wilson LM, Sharma R, Dy SM, Waldfogel JM, Robinson KA. Searching ClinicalTrials.gov did not change the conclusions of a systematic review. Journal of Clinical Epidemiology 2017;90:127-35.
67. Trinquart L, Abbe A, Ravaud P. Impact of reporting bias in network meta-analysis of antidepressant placebo-controlled trials. PloS One 2012;7:e35219.
68. Cameron C. Enhancing the use of network meta-analysis to synthesize information on benefits and harms of drugs to support regulatory and reimbursement decisions in Canada: School of Epidemiology, Public Health and Preventive Medicine University of Ottawa; 2015.
69. Ip S, Hadar N, Keefe S, et al. A web-based archive of systematic review data. Systematic Reviews 2012;1:15.
70. Li T, Vedula SS, Hadar N, Parkin C, Lau J, Dickersin K. Innovations in data collection, management, and archiving for systematic reviews. Annals of Internal Medicine 2015;162:287-94.
71. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-88.

72. Harris R, Bradburn M, Deeks J, Harbord R, Altman D, Sterne J. Metan: fixed- and random-effects meta-analysis. Stata Journal 2008;8:3-28.
73. White IR. Multivariate random-effects meta-regression: updates to mvmeta. Stata Journal 2011;11:255-270.
74. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PloS One 2013;8:e76654.
75. Chaimani A, Salanti G. Visualizing assumptions and results in network meta-analysis: The network graphs package. Stata Journal 2015;15:905-950.
76. White IR. Network meta-analysis. Stata Journal 2015;15:951-85.
77. Lumley T. Network meta-analysis for indirect treatment comparisons. Statistics In Medicine 2002;21:2313-24.
78. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Statistics in Medicine 2010;29:932-44.
79. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Research Synthesis Methods 2012;3:98-110.
80. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Research Synthesis Methods 2012;3:111-25.
81. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Medical decision making : an international journal of the Society for Medical Decision Making 2013;33:641-56.
82. Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. BMJ (Clinical Research Ed) 2012;344:d7202.
83. Roest AM, de Jonge P, Williams CD, de Vries YA, Schoevers RA, Turner EH. Reporting bias in clinical trials investigating the efficacy of second-generation antidepressants in the treatment of anxiety disorders: a report of 2 meta-analyses. JAMA Psychiatry 2015;72:500-10.
84. Curfman GD, Morrissey S, Drazen JM. Expression of concern reaffirmed. The New England Journal of Medicine 2006;354:1193.
85. Weatherall M, Aldington S, Caldwell B, Beasley R. Inconsistencies in cardiovascular data from COX-2 inhibitor trials--is it a class effect? Journal of the Royal Society of Medicine 2006;99:275-6.
86. Rising K, Bacchetti P, Bero L. Reporting bias in drug trials submitted to the Food and Drug Administration: review of publication and presentation. PLoS Medicine 2008;5:e217; discussion e.
87. Rodgers MA, Brown JV, Heirs MK, et al. Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion. BMJ (Clinical Research Ed) 2013;346:f3981.
88. Wieseler B, Wolfram N, McGauran N, et al. Completeness of reporting of patient-relevant clinical trial outcomes: comparison of unpublished clinical study reports with publicly available data. PLoS Medicine 2013;10:e1001526.
89. Schroll JB, Penninga EI, Gotzsche PC. Assessment of adverse events in protocols, clinical study reports, and published papers of trials of orlistat: A document analysis. PLoS Medicine 2016;13:e1002101.

90. Drugs@FDA frequently asked questions. U.S. Food and Drug Administration. (Accessed April 21, 2018, 2018, at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=faq.page.)
91. ClinicalTrials.gov Background. U.S. National Library of Medicine. (Accessed April 21, 2018, at https://www.clinicaltrials.gov/ct2/about-site/background.)
92. Stockmann C, Ross JS, Sherwin CMT, et al. Rate of asthma trial outcomes reporting on ClinicalTrials.gov and in the published literature. The Journal of Allergy and Clinical Immunology 2014;134:1443-6.
93. Stockmann C, Sherwin CM, Koren G, et al. Characteristics and publication patterns of obstetric studies registered in ClinicalTrials.gov. Journal of Clinical Pharmacology 2014;54:432-7.
94. Anderson ML, Chiswell K, Peterson ED, Tasneem A, Topping J, Califf RM. Compliance with results reporting at ClinicalTrials.gov. The New England Journal of Medicine 2015;372:1031-9.
95. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database--update and key issues. The New England Journal of Medicine 2011;364:852-60.
96. Halfpenny NJ, Quigley JM, Thompson JC, Scott DA. Value and usability of unpublished data sources for systematic reviews and network meta-analyses. Evidence-based Medicine 2016;21:208-13.
97. Bennett DA, Jull A. FDA: untapped source of unpublished trials. Lancet (London, England) 2003;361:1402-3.
98. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ (Clinical research ed) 2010;340:c332.
99. Li T. What's not shared—building on the FDA's transparency momentum. BMJ Opinion 2018.
100. International Conference on Harmonisation; Guideline on structure and content of clinical study reports; Availability. In: Administration FaD, ed. Federal Register 1996.

7 Tables

Table 1. Status of datasets used in this thesis

	Data sources		
	Bibliographic databases*	Drugs@FDA	ClinicalTrials.gov
Status of search	Completed in March 2014	Completed in April 2014	Completed in December 2016
Number of trials identified	104	28	27
Data extraction	Existing dataset	Only 16 of 28 (57%) trials reported sufficient data (point estimates and confidence intervals) for intraocular pressure outcome for our network meta-analysis).	Only 9/27 (33%) trials reported sufficient data (point estimates and confidence intervals) for intraocular pressure outcome for our network meta-analysis).

* CENTRAL within *The Cochrane Library*, PubMed, and EMBASE

Table 2. The extent of trial overlaps among bibliographic database, Drugs@FDA, and ClinicalTrials.gov

Match status	No. of trials	Biliographic databases Article reference ID¶	Drugs@FDA NDA-Protocol number	ClinicalTrials.gov Identifier
Three-way match	4	111*	204251 C-10-033	NCT01297517*
		112*	204251 C-10-039	NCT01297920*
			21398 190342-013T	NCT00332436
		84§	21398 190342-012T	NCT00332384
Two way match	10	39*	20869 47*	No match
		40*	20869 63*	No match
		74	21275 192024-008*	No match
		51*	21275 192024-009*	No match
		50*	20816 C-95-46*	No match
		44*	20816 C-95-48*	No match
		64*	21214 C97-UIOS-005*	No match
		56	21257 C-97-71*	No match
		60*	21257 C-97-72*	No match
		54	21257 C-97-79*	No match
	12	99*	No match	NCT00277498
		35*	No match	NCT00751049
		27*	No match	NCT00751062
		69*	No match	NCT00751127
		108*	No match	NCT01026831*
		110*	No match	NCT01155219
		109*	No match	NCT01253902
		104*	No match	NCT00539526
		113	No match	NCT00539526
		114*	No match	NCT01254604*
		101	No match	NCT00690794
		98	No match	NCT00991822
	1	No match	204251 C-09-038	NCT00961649*
No match	89	The remaining articles	No match	No match
	13	No match	20869 44*	No match
			20869 64*	
			21114 C-97-40*	
			21114 C-97-67*	
			21114 C-97-80*	
			21214 C97-UIOS-004*	
			21214 C97-UIOS-003	
			21257 C-97-73	
			21257 C-97-02	
			21262 190342-005	
			21275 192024-002	
			21275 192024-003	
			21275 192024-004	
	10	No match	No match	NCT00705757
				NCT00708422
				NCT00761319
				NCT00763061*
				NCT00798759
				NCT01001195
				NCT01110499
				NCT01310777*
				NCT01664039*
				NCT02140060*

Legend:

1. ¶ See Appendix 2 for reference ID
2. * Trial reports with sufficient data for NMA
3. § One article, two trials
4. The number of trial reports identified from bibliographic databases, Drugs@FDA, and ClinicalTrials.gov is 115, 28, 27 respectively.
5. Color coding:

Green	Three-way match
Yellow	Two-way match

Table 3.1. Characteristics of included trials (trials from bibliographic databases)

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/ low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
1	1983	Included	Included	NA	Excluded	NA	>=26 in both eyes	NR	NA	NA	NA	Placebo/ Vehicle/No treatment; Betaxolol	Yes	Yes	Can't tell	NR	1	20	NR
2	1984	Included	NA	NA	NA	Included	elevated IOPs	NR	Excluded	NA	Excluded	Betaxolol; Timolol	Yes	Yes	Multi (2)	United States	6	78	The statistical analysis was limited to eyes that reached the required pretreatment IOP level of 26 mm Hg.
3	1985	Included	Included	NA	NA	NA	NR	NR	NA	NA	NA	Placebo/ Vehicle/No treatment; Levobunolol	Yes	Yes	Can't tell	NR	3	17	NR
4	1985	Included	Included	NA	NA	NA	>=23 in each eye	>=18	Excluded	NA	Excluded	Levobunolol; Timolol	Yes	Yes	Can't tell	NR	15	92	NR
5	1985	Included	Included	NA	NA	NA	>=23	NR	Excluded	NA	Excluded	Levobunolol; Timolol	Yes	Yes	Can't tell	NR	15	85	NR
6	1985	Included	Included	NA	NA	NA	>=23 in each eye	NR	NA	NA	NA	Levobunolol; Timolol	Yes	Yes	Multi (NR)	NR	12	67	NR

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
7	1985	Included	Included	NA	NA	NA	>=23 in each eye	NR	Excluded	NA	NA	Levobunolol; Timolol	Yes	Yes	Can't tell	NR	12	45	NR
8	1986	Included	NA	NA	NA	NA	>=26 in at least one eye	NR	NA	NA	NA	Betaxolol; Timolol	Yes	Yes	Can't tell	NR	6	29	NR
9	1988	Included	Included	NA	NA	NA	NR	NR	NA	NA	NA	Levobunolol; Timolol	Yes	Yes	Can't tell	NR	12	72	NR
10	1988	Included	Included	NA	NA	NA	average measurement >25.5 and no measurement <22	adults	Excluded	Excluded	Excluded	Betaxolol; Timolol	Yes	Yes	Multi (3)	United States	6	28	Responders
11	1988	NA	Included	Excluded	NA	NA	>=22	NR	NA	NA	NA	Levobunolol; Timolol	Yes	Yes	Single	NR	3	25	Evaluable population; Safety population or safety analysis
12	1988	Included	Included	NA	NA	Included	>=22 in at least one eye?	NR	NA	NA	NA	Betaxolol; Levobunolol	Yes	Yes	Can't tell	NR	3	73	NR
13	1988	Included	Included	NA	NA	NA	>=21	NR	NA	NA	NA	Levobunolol; Timolol	Yes	Yes	Multi (2)	Canada	3	25	NR
14	1989	NA	Included	NA	NA	NA	>=22 and <=28 in at least one eye	NR	Excluded	NA	Excluded	Placebo/Vehicle/No treatment; Timolol	No	No	Single	United States	60	97	Intention-to-treat; Other

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
15	1989	NA	Included	NA	NA	NA	>24 and <35, and difference between two eyes <=3	>=40	Excluded	Excluded	Excluded	Placebo/Vehicle/No treatment; Timolol	Can't tell	No	Multi (2)	United States	61	64	NR
16	1989	Included	Included	NA	Excluded	Excluded	>=24	>=18	Excluded	Excluded	Excluded	Betaxolol; Timolol	Yes	Yes	Multi (16)	Japan	3	137	NR
17	1991	NA	Included	NA	NA	NA	>=22	>=45 and <=70	Excluded	NA	Excluded	Placebo/Vehicle/No treatment; Timolol	Can't tell	No	Can't tell	NR	73	137	Intention-to-treat; Other
18	1991	Included	Included	NA	NA	NA	exclude patients whose increased IOP was not controlled by a single-drug therapy	NR	NA	NA	NA	Levobunolol; Timolol	Yes	Yes	Multi (NR)	NR	3	70	Other
19	1992	Can't tell	Included	NA	NA	Excluded	NR	NR	Excluded	Excluded	NA	Levobunolol; Timolol	Yes	Yes	Multi (7)	NR	2	128	NR
20	1992	Included	NA	NA	NA	NA	>21	>=18 and <=80	Excluded	Excluded	Excluded	Carteolol; Timolol	Yes	Yes	Multi (NR)	NR	12	72	Compliers or Adheres
21	1993	Included	Included	Excluded	Excluded	Excluded	>=22 and <=35	NR	Excluded	NA	Excluded	Timolol; Unoprostone	Yes	Yes	Multi (18)	Japan	3	147	NR
22	1993	Included	Included	NA	NA	NA	NR	>=21	Excluded	Excluded	Excluded	Apraclonidine; Timolol	Yes	Yes	Multi (NR)	NR	3	56	NR
23	1993	Included	Included	NA	NA	NA	NR	NR	Excluded	NA	Excluded	Placebo/Vehicle/N	Yes	Yes	Multi (3)	United States	1	42	Per protocol

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
												o treatment; Dorzolamide							
24	1994	Included	Included	NA	NA	Included	>=22	NR	NA	NA	NA	Carteolol; Levobunolol	Yes	Yes	Multi (NR)	NR	3	52	NR
25	1994	Included	Included	NA	NA	NA	>=21 and <30 in each eye	>=20 and <=70	Excluded	Excluded	Excluded	Timolol; Dorzolamide	Yes	Yes	Multi (51)	Japan	3	218	NR
26	1994	NA	Included	NA	NA	NA	>=22 and <=30	NR	NA	NA	NA	Placebo/Vehicle/No treatment; Levobunolol	Can't tell	No	Can't tell	NR	24	49	NR
27	1995	Included	Included	NA	Excluded	Included	>=22	>=40	Excluded	Excluded	Excluded	Timolol; Latanoprost	Yes	Yes	Multi (13)	Sweden; Denmark; Finland; Norway	6	163	NR
28	1995	NA	Included	NA	NA	NA	>=21 and <35	NR	Excluded	Excluded	Excluded	Placebo/Vehicle/No treatment; Timolol	Can't tell	No	Single	United States	24	37	NR
29	1995	Included	Included	NA	NA	NA	>=23	>=21 and <=85	Excluded	NA	Excluded	Betaxolol; Timolol; Dorzolamide	Yes	Yes	Multi (34)	Costa Rica; Colombia; United States; Mexico; United Kingdom; Switzerland;	12	516	Intention-to-treat; Per protocol

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
																France; Austria; Australia; Holland; Germany; Peru; Brazil; Israel; Belgium; Argentina; Canada; Sweden; Portugal; New Zealand; Iceland			
30	1996	Included	Included	NA	Excluded	Included	>=22	>40	Excluded	Excluded	Excluded	Timolol; Latanoprost	Yes	Yes	Multi (NR)	Sweden	6	19	NR
31	1996	Included	Included	NA	NA	NA	NR	NR	Excluded	Excluded	Excluded	Timolol; Latanoprost	No	Yes	Multi (35)	Japan	3	154	NR
32	1996	Included	Included	NA	NA	NA	post-washout IOP >=23 mmHg and <35 mmHg in each eye; excluded IOP asymmetry of more	adults	Excluded	Excluded	Excluded	Brimonidine; Timolol	Yes	Yes	Multi (NR)	NR	12	647	Safety population or safety analysis

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
							than 5 mmHg												
33	1996	Included	Included	NA	NA	NA	>=22 and <=34, and difference between two eyes <=5	>=21	Excluded	Excluded	Excluded	Brimonidine; Betaxolol	Yes	Yes	Multi (13)	United States	3	177	Per protocol; Safety population or safety analysis
34	1996	Included	Included	NA	NA	NA	>=22 and <=35, and difference between two eyes <=4	adults	Excluded	Excluded	Excluded	Apraclonidine; Timolol	Yes	Yes	Multi (16)	United States	3	171	NR
35	1996	Included	Included	NA	Excluded	Included	>=22	>=40	Excluded	Excluded	Excluded	Timolol; Latanoprost	Yes	Yes	Multi (14)	United Kingdom	6	255	NR
36	1996	Included	Included	NA	NA	NA	NR	>=40 and <=70	Excluded	NA	Excluded	Carteolol; Timolol	Yes	No	Multi (3)	Japan	4	33	NR
37	1997	Included	Included	NA	NA	NA	<=20 in both eyes and difference between two eyes <=4, and IOP fluctuation between both	>=20 and <=75	Excluded	Excluded	Excluded	Levobunolol; Timolol	Yes	No	Multi (24)	Japan	3	90	Intention-to-treat

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
							eyes=<2 at baseline and 6 weeks prior to the study												
38	1997	Included	Included	NA	NA	Excluded	>=22 and <=34, and difference between two eyes <5	>=18 and <=85	Excluded	Excluded	NA	Cartelol; Timolol	Yes	Yes	Multi (13)	United States	3	163	Intention-to-treat
39	1997	Included	Included	NA	Excluded	Included	>=21	NR	Excluded	Excluded	Excluded	Timolol; Latanoprost	Yes	Yes	Multi (NR)	France	1	33	NR
40	1998	Included	Included	NA	Excluded	NA	NR	>=21 and <=85	Excluded	Excluded	Excluded	Timolol; Dorzolamide	No	Yes	Multi (27)	United States	3	220	Per protocol; Other
41	1998	Included	NA	NA	Excluded	Included	>=25 with IOP-reducing therapy or >=30 without IOP-reducing therapy	>=18	Excluded	Excluded	Excluded	Timolol; Latanoprost	Yes	No	Multi (13)	Germany	1	37	NR
42	1998	Included	Included	NA	NA	Excluded	>=23 and <=35, and difference	>=21	Excluded	Excluded	Excluded	Brimonidine; Timolol	Yes	Yes	Multi (NR)	NR	12	306	Per protocol; Safety population or

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
							between two eyes <=5												safety analysis
43	1998	Included	Included	NA	Excluded	NA	>=23 in at least one eye?	>=21	Excluded	NA	Excluded	Betaxolol; Dorzolamide	Yes	Yes	Multi (24)	United States	3	310	Per protocol; At least receiving one treatment
44	1998	Included	Included	Excluded	Excluded	Included	NR	>=21	Excluded	Excluded	Excluded	Timolol; Brinzolamide; Dorzolamide	Yes	Yes	Multi (42)	United States; Germany; France; Belgium; Portugal; the Netherlands; Iceland	3	347	Intention-to-treat; Per protocol; Responders; At least receiving one treatment; Safety population or safety analysis
45	1999	Included	Included	NA	Excluded	NA	>=22 at 9AM and 11AM	>=21	Excluded	Excluded	Excluded	Timolol; Dorzolamide	Yes	No	Multi (22)	United States	3	149	Per protocol; Safety population or safety analysis; Other
46	1999	Included	NA	NA	NA	NA	NR	NR	NA	NA	NA	Betaxolol; Timolol	No	Yes	Can't tell	NR	3	40	NR
47	1999	Included	Included	NA	NA	Excluded	NR	NR	Excluded	Excluded	Excluded	Carteolol; Timolol	Yes	Yes	Multi (NR)	United States	3	112	Intention-to-treat
48	1999	NA	Included	NA	NA	NA	>=20 and <=40	NR	Excluded	Excluded	Excluded	Placebo/Vehicle/No	Yes	No	Single	United States	1	56	NR

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
												treatment; Brimonidine							
49	2000	Included	Included	NA	NA	Included	NR	>40	NA	NA	NA	Timolol; Latanoprost	Can't tell	No	Multi (13)	Sweden	6	243	NR
50	2000	Included	Included	NA	Excluded	Included	NR	NR	Excluded	Excluded	Excluded	Dorzolamide; Latanoprost	Yes	Yes	Multi (12)	NR	3	213	NR
51	2000	Included	Included	Excluded	Excluded	Included	>=24 and <=36 at 8AM and >= 21 and <= 36 mmHg at 10AM and 6PM	>=21	Excluded	Excluded	Excluded	Placebo/Vehicle/No treatment; Brinzolamide; Dorzolamide	Yes	Yes	Multi (24)	United States	3	285	Intention-to-treat; Per protocol; Safety population or safety analysis
52	2001	Included	Included	NA	NA	NA	>=22 and <=34	>=18	Excluded	Excluded	Can't tell	Brimonidine; Latanoprost	Yes	Yes	Multi (5)	United States	3	125	Per protocol
53	2001	NA	Included	NA	NA	NA	>=21 and <=29 in each eye	>=20 and <=79	Excluded	Excluded	Excluded	Latanoprost; Unoprostone	No	No	Can't tell	NR	2	36	Safety population or safety analysis; Other
54	2001	Included	Included	NA	Excluded	NA	>=21	>=18	Excluded	Excluded	Excluded	Latanoprost; Unoprostone	Yes	Yes	Single	Brazil	2	105	Intention-to-treat; Per protocol
55	2001	Included	Included	NA	NA	NA	>=22 and <=34 at 8 AM	>=21	Excluded	Excluded	Excluded	bimatoprost/timolol	Yes	Yes	Multi (30)	United States, Australi	12	596	Intention-to-treat

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
							on day 0 after washout									a, New Zealand			
56	2001	Included	Included	NA	NA	Included	>=24 to <=36 in the same eye(s), at the 8 AM at two eligibility visits, at least 7 days apart.	NR	Excluded	Excluded	Excluded	travoprost/latanoprost/timolol	Yes	Yes	Multi (NR)	United States	12	801	Intention-to-treat, Per protocol, Safety Population
57	2001	Included	Included	NA	Excluded	Included	>=24 and <=36 at 9 AM, and >=21 and <=36 in the same eye at 11 AM and 4 PM, on two eligibility visits, after washout	NR	Excluded	Excluded	Excluded	travoprost/timolol	Yes	Yes	Multi (64)	Australia, Belgium, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Netherland, Norway, Portugal, Spain, Sweden, Switzerland, UK	9	573	Intention-to-treat, Per protocol, Safety Population
58	2002	Included	Included	NA	Excluded	Excluded	>21	>=21	Excluded	Excluded	Excluded	Latanoprost;	No	No	Multi (2)	Singapore	2	32	NR

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
												Unoprostone							
59	2002	Included	NA	NA	Included	NA	excluded mean IOP of two eyes >30 or any IOP >35 in one eye	NR	Excluded	Excluded	Excluded	Placebo/Vehicle/No treatment; Dorzolamide	No	No	Single	Sweden	1	47	Intention-to-treat
60	2002	Included	Included	NA	NA	Included	>=24 and <=36	>=21	Excluded	Excluded	Excluded	Timolol; Travoprost	Yes	Yes	Multi (44)	United States	6	396	Intention-to-treat; Per protocol; Safety population or safety analysis
61	2002	Included	Included	NA	Excluded	Included	>=25 with IOP-reducing therapy or >=30 without IOP-reducing therapy	>=18	Excluded	Excluded	Excluded	Timolol; Latanoprost	Yes	No	Multi (38)	United States	12	280	Intention-to-treat; Safety population or safety analysis
62	2002	Included	Included	NA	Excluded	NA	>=21	>=18	Excluded	Excluded	Excluded	Latanoprost; Unoprostone	Yes	Yes	Multi (24)	United States	2	164	Intention-to-treat; Safety population or safety analysis
63	2002	Included	Included	NA	Excluded	Included	NR	NR	Excluded	Excluded	Excluded	Brimonidine;	Yes	Yes	Multi (30)	Germany;	6	375	Intention-to-treat

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
												Latanoprost				United Kingdom; Spain; Finland			
64	2002	Included	Included	NA	NA	Included	NR	adults	Excluded	Excluded	Excluded	Betaxolol; Timolol; Unoprostone	Yes	Yes	Multi (27)	Europe; Israel	24	556	Intention-to-treat
65	2002	Included	Included	NA	Excluded	Included	>=25 with IOP-reducing therapy or >=30 without IOP-reducing therapy	>=18	Excluded	Excluded	Excluded	Timolol; Latanoprost	Yes	No	Multi (37)	NR	6	296	Intention-to-treat; At least receiving one treatment
66	2002	Included	Included	NA	NA	NA	>=18 and <=34, and difference between two eyes <=5	>=21	NA	NA	NA	Brimonidine; Latanoprost	Yes	No	Multi (14)	United States	3	107	NR
67	2002	Included	Included	NA	Excluded	NA	>=21 and <=27, and difference between two eyes <2	>=18	Excluded	NA	Excluded	Latanoprost; Unoprostone	Yes	Yes	Single	United States	1	50	NR
68	2002	NA	NA	NA	NA	NA	>=21 and <30	NR	Excluded	NA	Excluded	Latanoprost;	Yes	Yes	Multi (10)	Japan	2	44	NR

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
												Unoprostone							
69	2003	Included	Included	Can't tell	Can't tell	Can't tell	NR	NR	Can't tell	Can't tell	Can't tell	Timolol; Latanoprost	Yes	Yes	Multi (17)	United States	6	268	Intention-to-treat; Responders
70	2003	Included	NA	Excluded	Excluded	Excluded	>20	>=40 and <=60	NA	NA	NA	Latanoprost; Travoprost	No	No	Single	Italy	6	18	NR
71	2003	Included	Included	NA	NA	NA	NR	NR	Excluded	Excluded	Excluded	Brimonidine; Latanoprost	Yes	Yes	Can't tell	NR	3	38	NR
72	2003	NA	Included	NA	NA	NA	>=22 and <=35	>35	NA	NA	NA	Placebo/Vehicle/No treatment; Betaxolol	Can't tell	No	Single	United Kingdom	37	255	Intention-to-treat
73	2003	Included	Included	NA	Excluded	Included	>=21	>=18	Excluded	Excluded	Excluded	Bimatoprost; Latanoprost; Travoprost	Yes	Yes	Multi (45)	United States	3	410	Intention-to-treat; Per protocol; Safety population or safety analysis
74	2003	Included	Included	NA	NA	NA	>22mm Hg and<34 mmHg at 8 am on baseline after washout	>=21	Excluded	Excluded	Excluded	bimatoprost/timolol	Yes	Yes	Multi (31)	United States and Canada	6	602	Intention-to-treat
75	2004	Included	NA	NA	NA	NA	NR	NR	Excluded	NA	Excluded	Betaxolol;	No	No	Can't tell	NR	3	31	NR

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
												Latanoprost							
76	2004	Included	NA	NA	NA	NA	NR	NR	NA	NA	NA	Placebo/Vehicle/No treatment; Unoprostone	Yes	No	Single	NR	2	50	NR
77	2004	Included	Included	Excluded	Excluded	Excluded	<16 on timolol for 12 months	>=40 and <=60	NA	NA	NA	Timolol; Bimatoprost	Can't tell	No	Single	Italy	6	38	NR
78	2004	Included	Included	NA	NA	NA	>=22 and <=34, and difference between two eyes <=5	adults	Excluded	Excluded	Excluded	Timolol; Bimatoprost; Latanoprost	Yes	Yes	Multi (7)	United States	1	115	Intention-to-treat; Modified intention-to-treat; Safety population or safety analysis
79	2004	Included	NA	NA	Excluded	NA	>=20 and <=30	NR	NA	NA	NA	Timolol; Brinzolamide	Yes	Yes	Single	Taiwan	1	48	NR
80	2005	Included	Included	Excluded	Excluded	Excluded	NR	>=18	Excluded	Excluded	Excluded	Timolol; Travoprost	Yes	Yes	Multi (33)	United States	3	176	Intention-to-treat
81	2005	Included	Included	NA	Excluded	NA	>=22	>=18	Excluded	Excluded	Excluded	Brimonidine; Latanoprost	Yes	Yes	Multi (23)	United States	6	301	Intention-to-treat; Per protocol; Safety population or safety analysis

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
82	2005	NA	Included	NA	NA	NA	>=22 and <=29 in at least one eye?	>=30 and <=80	Excluded	NA	Excluded	Placebo/Vehicle/No treatment; Dorzolamide	Yes	Yes	Multi (18)	Belgium; Germany; Italy; Portugal	61	976	Intention-to-treat; Safety population or safety analysis
83	2006	Included	NA	NA	NA	NA	NR	NR	Excluded	Excluded	Excluded	Betaxolol; Latanoprost	No	No	Can't tell	NR	3	40	NR
84	2006	Included	Included	NA	NA	Can't tell	NR	>=18	NA	NA	NA	brimonidine/timolol	Yes	Yes	Multi (53)	United States	12	1159	Intention-to-treat; Per protocol;
85	2007	Included	Included	NA	NA	NA	>=22 and <=36	>=18	Excluded	Excluded	Excluded	Bimatoprost; Latanoprost; Travoprost	No	No	Can't tell	NR	6	60	Other
86	2007	Included	Included	NA	NA	Included	>=24 and <=34	>18	Excluded	Excluded	Excluded	Timolol; Bimatoprost	Yes	Yes	Can't tell	Spain	6	60	NR
87	2008	Included	NA	NA	NA	Included	<=36	>=18	Excluded	Excluded	Excluded	Bimatoprost; Travoprost	No	No	Single	Turkey	6	82	NR
88	2008	Included	Included	NA	Included	NA	>=18 with IOP-reducing medication or >=24 for treatment naïve patients	adults	Excluded	Excluded	Excluded	Timolol; Bimatoprost	Yes	Yes	Multi (59)	United States; Canada	3	528	Intention-to-treat

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
							in at least one eye												
89	2008	Included	Included	NA	Excluded	Included	>=18 at 8AM or >=21 at 10AM and <=36 in at least one eye	>=18	Excluded	Excluded	Excluded	Timolol; Brinzolamide	Yes	Yes	Multi (35)	United States	6	346	Intention-to-treat; Per protocol
90	2008	Can't tell	Included	Can't tell	Can't tell	Can't tell	>=22 and <=34	NR	NA	NA	NA	Timolol; Bimatoprost	Yes	Yes	Multi (15)	United States	49	152	Intention-to-treat; Per protocol; At least receiving one treatment; Safety population or safety analysis
91	2008	Included	NA	NA	Excluded	NA	>22	>=18	Excluded	NA	Excluded	Bimatoprost; Latanoprost; Travoprost	No	No	Can't tell	NR	2	48	NR
92	2009	Can't tell	Included	Can't tell	Can't tell	Can't tell	>=17 and <=22 in each eye	>=18	Excluded	NA	Excluded	Bimatoprost; Latanoprost	Yes	No	Multi (8)	Australia	6	208	Intention-to-treat; Safety population or safety analysis
93	2009	Included	NA	NA	NA	Excluded	>21	NR	NA	NA	NA	Brimonidine;	Yes	No	Single	Brazil	1	50	NR

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
												Timolol; Travoprost							
94	2009	Included	NA	Included	NA	NA	NR	>=40 and <=80	Excluded	NA	Excluded	Betaxolol; Levobunolol; Timolol	Yes	No	Single	India	3	62	NR
95	2009	Included	Included	NA	NA	NA	>=22	>=18 and <=70	Excluded	Excluded	Excluded	Timolol; Travoprost	Yes	Yes	Can't tell	China	3	64	NR
96	2010	Included	Included	NA	NA	Included	NR	>=18	Excluded	Excluded	Excluded	Latanoprost/travoprost	Yes	No	Multi (66)	United States	3	678	Intention-to-treat
97	2010	Included	Included	NA	NA	Included	>23 and <36	NR	Excluded	Excluded	Excluded	Bimatoprost; Latanoprost; Travoprost	Yes	Yes	Multi (9)	Canada	6	83	Per protocol
98	2010	NA	Included	NA	NA	NA	difference between two eyes <=5	>=18	Excluded	Excluded	NA	Placebo/Vehicle/No treatment; Bimatoprost	Yes	No	Multi (15)	United States	1	218	Modified intention-to-treat
99	2010	Included	Included	NA	Excluded	Included	>=26 and <=36	>=18	Excluded	Excluded	Excluded	Timolol; Latanoprost	Yes	Yes	Multi (58)	United States	3	265	Intention-to-treat; At least receiving one treatment; Eligible population; Safety population or safety analysis

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
100	2010	Can't tell	Included	Can't tell	Can't tell	Can't tell	Inadequate IOP control after at least 30 days on latanoprost monotherapy, judged by the investigator	adults	Excluded	NA	Excluded	Bimatoprost; Travoprost	Yes	No	Multi (17)	NR	3	260	Intention-to-treat
101	2010	Included	Included	Excluded	Excluded	Can't tell	>=21 and <=35 in each eye	>=18	Excluded	NA	Excluded	Bimatoprost; Travoprost	Yes	Yes	Multi (NR)	Egypt	6	72	NR
102	2010	Included	Included	NA	NA	Included	>=22 and <=34 in at least one eye	>=18	Excluded	NA	Excluded	Latanoprost; Taflupros t	Yes	Yes	Multi (3)	Italy; Finland	1	36	Intention-to-treat; At least receiving one treatment; Safety population or safety analysis
103	2010	Included	Included	NA	NA	Can't tell	NR	>=18	NA	NA	NA	bimatoprost /latanoprost/travoprost	Yes	Yes	Multi (9)	United States	3	99	Per protocol
104	2010	Included	Included	NA	Excluded	Excluded	>=21	NR	Excluded	Excluded	Excluded	Timolol/dorzolamide	Yes	Yes	Single	Austria	6	140	NR

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
105	2011	NA	NA	NA	NA	NA	NR	NR	NA	NA	NA	Placebo/Vehicle/No treatment; Brinzolamide	Can't tell	No	Single	China	27	96	NR
106	2011	Included	Included	NA	Excluded	Excluded	>=21 and <=35 if not controlled, or <=21 on beta-blocker monotherapy	NR	Can't tell	Excluded	Can't tell	Latanoprost; Travoprost	Yes	Yes	Single	China	1	90	NR
107	2012	Included	Included	NA	NA	NA	=<31 in both eyes; >= 18 for POAG patients; >=22 for OHT patients	>=20	Excluded	NA	Excluded	Brimonidine; Timolol	Yes	Yes	Multi (51)	Japan	1	196	At least receiving one treatment; Safety population or safety analysis
108	2012	Included	Included	NA	NA	Included	>=23 and <=36, and difference between two eyes <5	>=18	Excluded	NA	Excluded	Timolol; Taflupost	Yes	Yes	Multi (50)	United States; Spain; Switzerland	3	610	Per protocol; At least receiving one treatment
109	2013	Included	Included	NA	NA	NA	NR	>=18	Excluded	NA	NA	Bimatoprost; Travoprost	Yes	Yes	Multi (15)	Canada; United States	3	109	Intention-to-treat; Per protocol;

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
																			Safety population or safety analysis
110	2013	Included	Included	Excluded	Excluded	Excluded	<=18	>=18 and <=90	NA	NA	NA	Timolol; Latanoprost	Yes	No	Multi (45)	France	3	143	Per protocol; Other
111	2013	Included	Included	Excluded	Excluded	Excluded	>=24 and <=36 at 8AM and >=21 and <=36 at 10AM; <36 in both eyes at all time points	>=18	Excluded	Excluded	Excluded	Brimonidine; Brinzolamide	Yes	Yes	Multi (66)	United States	3	405	Intention-to-treat; Safety population or safety analysis
112	2013	Included	Included	NA	Excluded	NA	>=24 and <=36 at 8AM and >=21 and <=36 at 10AM; <36 in both eyes at all time points	>=18	Excluded	Excluded	Excluded	Brimonidine; Brinzolamide	Yes	Yes	Multi (65)	United States	6	445	Intention-to-treat; Safety population or safety analysis
113	2014	Included	Included	NA	NA	Included	NR	>=18	NA	NA	NA	latanoprostene bunod/latanoprost	Yes	Yes	Multi (23)	United States and European Union	1	413	Intention-to-treat, safety population

Reference ID¶	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/ low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months)	Number of participants or eyes included in our analysis	Types of analysis
114	2016	Included	Included	NA	NA	Included	NR	>=18 and <=80	NA	NA	NA		Yes	Yes	Multi (12)	India	1	164	Per protocol

Legend:
1. ¶ See Appendix 2 for reference ID
2. * Only showing drugs eligible for our systematic review
3. NA: not applicable
4. NR: not report
5. IOP: intraocular pressure

Table 3.2. Characteristics of included trials (trials from Drugs@FDA)

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
204251 C-09-038	2012	Included	Included	NA	NA	Can't tell	NR	>=18	NA	NA	NA	Brinzolamide; Brimonidine	Can't tell	Can't tell	Multi (9)	NR	1.5	170	Intention-to-treat; Per protocol; Safety population or safety analysis
204251 C-10-033	2012	Included	Included	Excluded	Excluded	Excluded	Greater than or equal to 24 mmHg and less than or equal to 36 mmHg at the 8 AM time point at both Eligibility Visit 1 and Eligibility Visit 2; Greater than or equal to 21 mmHg and less than or equal to 36 mmHg at the 10AM time point at at both Eligibility Visit 1 and Eligibility Visit 2;The mean IOP in either eye must not have been greater than 36 mmHg at any time point.	>=18	Excluded	Excluded	Excluded	Brinzolamide; Brimonidine	Yes	No	Multi (68)	United States	3	660	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
204251 C-10-039	2012	Included	Included	Excluded	Excluded	Excluded	Greater than or equal to 24 mmHg and less than or equal to 36 mmHg at the 8 AM time point at both Eligibility Visit 1 and Eligibility Visit 2; Greater than or equal to 21 mmHg and less than or equal to 36 mmHg at the 10AM time point at both Eligibility Visit 1 and Eligibility Visit 2; The mean IOP in either eye must not have been greater than 36 mmHg at any time point.	>=18	Excluded	Excluded	Excluded	Brinzolamide; Brimonidine	Yes	No	Multi (64)	United States	6	690	Intention-to-treat; Per protocol; Safety population or safety analysis
20816 C-95-46	1997	Included	Included	NA	NA	NA	Qualifying IOPs following wash-out, were 24 to 36 mmHg, inclusive, in at least one eye, at the 8:00 am. measurement and 21 to 36 mmHg, inclusive, at 10:00 am. and 6;00 p.m.; with no greater than a 5 mm: Hg difference between eyes during eligibility visits 1 and 2.	>=21	NA	NA	NA	Brinzolamide; Dorzolamide; Placebo/ Vehicle/ No treatment	Yes	Yes	Multi (29)	United States	3	463	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/ single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
20816 C-95-48	1997	Included	Included	NA	NA	NA	Qualifying IOPs following wash-out, were 24 to 36 mmHg, inclusive, in at least one eye, at the 8:00 am. measurement and 21 to 36 mmHg, inclusive, at 10:00 am. and 6;00 p.m.; with no greater than a 5 mmHg difference between eyes during eligibility visits 1 and 2.	>=21	NA	NA	NA	Brinzolamide; Dorzolaimde; Timolol	Yes	Yes	Multi (46)	United States; Germany; France; Belgium; Portugal; Netherlands; Iceland	3	572	Intention-to-treat; Per protocol; Safety population or safety analysis
20869 44	1997	Included	Included	NA	NA	NA	IOP >= 24 mmHg in at least one eye at hour 0 and hour 2, following washout of ocular hypotensive medication	21-85	NA	NA	NA	Dorzolamide; Timolol	Yes	Yes	Multi (22)	South Africa; Belgium; Brazil; France; Peru; Austria; Costa Rica; New Zealand; Portugal; Germany; Colombia; Australia; Netherlands;	15	350	All patients-treated analysis

Drugs@FDA NDA-ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
																Argentina			
20869 47	1997	Included	Included	NA	NA	NA	IOP >= 24 mmHg in at least one eye at hour 0 and hour 2, following washout of ocular hypotensive medication	21-85	NA	NA	NA	Dorzolamide; Timolol	Yes	Yes	Multi (27)	United States	3	335	All patients-treated analysis
20869 63	1997	Included	Included	NA	NA	NA	IOP >= 22 mmHg in at least one eye at hour 0 and hour 2, at baseline following the 3 week run-in period	>=21	NA	NA	NA	Dorzolamide; Timolol	Can't tell	No	Multi (23)	United States	3	253	All patients-treated analysis
20869 64	1997	Included	Included	NA	NA	NA	IOP >= 22 mmHg in at least one eye at hour 0 and hour 2, at baseline following the 3 week run-in period	>=21	NA	NA	NA	Dorzolamide; Timolol	Can't tell	No	Multi (23)	United States	3	247	All patients-treated analysis
21114 C-97-40	1999	Included	Included	Excluded	c	Included	Mean IOP measurements must be 24 to 36 mmHg, inclusive, in at least one eye, the same eye, at the 8:00 a.m. IOP measurements at both Eligibility Visits 1 and 2. Additionally, the 10:00 a.m. mean IOP measurement must	NR	Excluded	Excluded	Excluded	Levobetaxolol; Betaxolol; Timolol; Placebo/ Vehicle/ No treatment	Yes	Yes	Multi (18)	United States	1	256	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/ single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
							be 21 to 36 mmHg, inclusive, in at least one eye, the same eye that qualified previously. Mean IOP measurements in each eye must be less than or equal to 36 mmHg at all times. These IOP criteria must be met at both Eligibility Visits l and 2.												
21114 C-97-67	1999	Included	Included	Excluded	Excluded	Included	Mean IOP measurements must be 24 to 36 mmHg, inclusive, in at least one eye, the same eye, at the 8:00 a.m. IOP measurements at both Eligibility Visits 1 and 2. Additionally, the 10:00 a.m. mean IOP measurement must be 21 to 36 mmHg, inclusive, in at least one eye, the same eye that qualified previously. Mean IOP measurements in each eye must be less than or equal to 36 mmHg at all times. These IOP criteria must be met at both Eligibility Visits l and 2.	NR	Excluded	Excluded	Excluded	Levobetaxolol; Timolol	Yes	Yes	Multi (24)	United States	3	359	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/ single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
21114 C-97-80	1999	Included	Included	Excluded	Excluded	Included	Mean IOP measurements must be 24 to 36 mmHg, inclusive, in at least one eye, the same eye, at the 8:00 a.m. IOP measurements at both Eligibility Visits 1 and 2. Additionally, the 10:00 a.m. mean IOP measurement must be 21 to 36 mmHg, inclusive, in at least one eye, the same eye that qualified previously. Mean IOP measurements in each eye must be less than or equal to 36 mmHg at all times. These IOP criteria must be met at both Eligibility Visits l and 2.	NR	Excluded	Excluded	Excluded	Levobetaxolol; Timolol	Yes	Yes	Multi (25)	United States	3	348	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
21214 C97-UIOS-004	2000	Included	Included	Excluded	Excluded	Excluded (except for pseudoexfoliation)	Inclusion: had a post washout or untreated IOP>=22mmHg and =<30mmHg in the eligible eye(s) at one or more time points during the baseline 12-hour diurnal IOP elevation. In subjects with bilateral POAG or OH, both eyes had to meat IOP criteria at the same baseline 12-hour diurnal time point. Exclusion: difference in IOP measurements at any one time point during the baseline 12-hour diurnal IOP elevation was greater than 5 mmHg between eyes in subjects diagnosed with bilateral POAG or OH.	>=18	Excluded	Excluded	Excluded	Unoprostone; Timolol	Yes	Yes	Multi (30)	United States	6	571	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
21214 C97-UIOS-005	2000	Included	Included	Excluded	Excluded	Excluded (except for pseudoexfoliation)	Inclusion: a post-washout or untreated IOP>=22mmHg and =<30mmHg in the eligible eye(s) at one or more time points during the baseline 12-hour diurnal IOP evaluation. For subjects with bilateral POAG or OH, both eyes had to meet IOP criteria at the same baseline 12-hour diurnal time point. Exclusion: the difference in IOP measurements at any one time point during the Baseline 12-hour diurnal IOP elevation was greater than 5 mmHg between eyes in subjects with bilateral POAG or OH.	>=18	Excluded	Excluded	Excluded	Unoprostone; Timolol; Betaxolol	Yes	Yes	Multi (28)	United Kingdom; Sweden; Italy; netherlands; Belgium; Germany; Israel; France; Spain; Switzerland	6	556	Intention-to-treat; Per protocol; Safety population or safety analysis
21214 C97-UIOS-003	2000	Included	Included	NA	NA	NA	morning IOP of 23 to 34 mmHg, inclusive at baseline visit after washout of prior therapy for glaucoma or OHT with no more than a 5 mmHg difference between eyes	NR	NA	NA	NA	Unoprostone; Timolol; Placebo/ Vehicle/ No treatment	Yes	Yes	Multi (7)	United States	1	237	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/ single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
21257 C-97-71	2000	Included	Included	Excluded	Excluded	Included	Each qualifying eye(s) must have 24 to 36 mmHg IOP at 8AM on both eligibility visit days, 21 to 36 mmHg mean IOP at 10AM and 4PM on both eligibility visit days(the mean IOP is the average of two IOP measurements in the same eye); the same eye(s) must qualify at both eligibility visits; the mean IOP in either eye at any eligibility exam visit must not be greater than 36 mmHg	NR	Excluded	Excluded	Excluded	Travoprost; Timolol; latanoprost	Yes	Yes	Multi (44)	United States	12	801	Intention-to-treat; Per protocol; Safety population or safety analysis
21257 C-97-72	2000	Included	Included	Excluded	Excluded	Included	Each qualifying eye(s) must have 24 to 36 mmHg IOP at 8AM on both eligibility visit days, 21 to 36 mmHg mean IOP at 10AM and 4PM on both eligibility visit days (the mean IOP is the average of two IOP measurements in the same eye); the same eye(s) must qualify at both eligibility visits; the mean IOP in either eye at any eligibility exam visit	NR	Excluded	Excluded	Excluded	Travoprost; Timolol	Yes	Yes	Multi (44)	United States	6	605	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
							must not be greater than 36 mmHg												
21257 C-97-73	2000	Included	Included	Excluded	Excluded	Included	Each qualifying eye(s) must have 24 to 36 mmHg IOP at 8AM on both eligibility visit days, 21 to 36 mmHg mean IOP at 10AM and 4PM on both eligibility visit days(the mean IOP is the average of two IOP measurements in the same eye); the same eye(s) must qualify at both eligibility visits; the mean IOP in either eye at any eligibility exam visit must not be greater than 36 mmHg	NR	Excluded	Excluded	Excluded	Travoprost; Placebo/ Vehicle/ No treatment	Yes	No	Multi (46)	United States	6	427	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
21257 C-97-79	2000	Included	Included	Excluded	Excluded	Included	Each qualifying eye(s) must have 24 to 36 mmHg IOP at 8AM on both eligibility visit days, 21 to 36 mmHg mean IOP at 10AM and 4PM on both eligibility visit days (the mean IOP is the average of two IOP measurements in the same eye); the same eye(s) must qualify at both eligibility visits; the mean IOP in either eye at any eligibility exam visit must not be greater than 36 mmHg	NR	Excluded	Excluded	Excluded	Travoprost; Timolol	Yes	Yes	Multi (64)	Australia; Belgium; Denmark; Finland; France; Germany; Iceland; Italy; Netherlands; Norway; Portugal; Sweden; Switzerland; United Kingdom	9	573	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/ single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
21257 C-97-02	2000	Included	Included	NA	NA	Included	Entry mean IOP of 24 to 36 mmHg, inclusive, in one eye, the same eye, at the post washout 8AM IOP measurement at both Eligibility Visits I and 2. Additionally, the 10AM, 12N, 4PM, and SPM mean IOP measurements must be 21 to 36 mmHg, inclusive, in one eye, the same eye that previously qualified. Mean IOP measurements at both Eligibility Visits I and 2 must be Jess than or equal to 36 mmHg at all times.	>=21	NA	NA	NA	Travoprost; Placebo/ Vehicle/ No treatment	Yes	Yes	Multi (9)	United States	1	227	Intention-to-treat; Per protocol; Safety population or safety analysis
21262 190342-005	2000	Included	Included	Excluded	Included	Included	Baseline (day 0) hour 0 IOP of >= 23 mm Hg and <= 34 mm Hg in each eye and asymmetry of IOP not greater than 5 mm Hg	>=21	Excluded	Excluded	Excluded	Brimonidine; Timolol	Yes	Yes	Multi (5)	United States	1	122	Intention-to-treat; Per protocol
21275 192024-008	2001	Included	Included	NA	Included	Included	Day 0, hour 0 IOP >= 22 mm Hg and <= 34 mm Hg in each eye.	>=21	Excluded	Excluded	Excluded	Bimatoprost; Timolol	Yes	Yes	Multi (31)	United States	12	602	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/ single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
21275 192024-009	2001	Included	Included	NA	Included	Included	Day 0, hour 0 IOP >= 22 mm Hg and <= 34 mm Hg in each eye.	>=21	Excluded	Excluded	Excluded	Bimatoprost; Timolol	Yes	Yes	Multi (30)	United States	12	596	Intention-to-treat; Per protocol; Safety population or safety analysis
21275 192024-002	2001	Included	Included	NA	NA	Included	Post-washout(8AM) IOPs of greather than or equal to 23 mmHg and less then or equal to 34 mmHg in each eye and asymmetry of IOP between the eyes not greater than 5 mmHg; 8PM IOP on Day 0 more than 4 mmHg higher than the 8AM IOP(inclusion)	>=21	Excluded	Excluded	Excluded	Bimatoprost; Timolol; Placebo/ Vehicle/ No treatment	Yes	Yes	Single	United States	1	100	NR
21275 192024-003	2001	Included	Included	NA	NA	NA	Post-washout IOP>=23mmHg and =<34mmHg in each eye and between-eye asymmetry of IOP=< 5mmHg	>=21	Excluded	Excluded	Excluded	Bimatoprost; Placebo/ Vehicle/ No treatment	Yes	Yes	Single	United States	1	32	Intention-to-treat; Per protocol; Safety population or safety analysis

Drugs@FDA NDA - ProtoCol Number	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age (years)	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared*	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/ single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up (months	Number of participants or eyes included	Types of analysis
21275 192024-004	2001	Included	Included	Excluded	Excluded	Excluded	Day 0 IOP at 8 AM greater than or equal to 23 mm Hg and less than or equal to 34 mm Hg in each eye and asymmetry of IOP between the eyes not greater than 5 mm Hg.	>=21	Excluded	Excluded	Excluded	Bimatoprost; Latanoprost; Placebo/ Vehicle/ No treatment	Yes	Yes	Multi (4)	United States	1	106	NR
21398 190342-012T	2007	Included	Included	NA	Included	Included	Baseline (day 0, hour 0), IOP >=22 mm Hg and <=34 mm Hg in each eye and asymmetry of IOP not greater than 5 mm Hg.	>=18	Excluded	Excluded	Excluded	Brimonidine; Timolol	Yes	Yes	NR	NR	12	573	Intention-to-treat
21398 190342-013T	2007	Included	Included	NA	Included	Included	Baseline (day 0, hour 0), IOP >=22 mm Hg and <=34 mm Hg in each eye and asymmetry of IOP not greater than 5 mm Hg.	>=18	NA	NA	NA	Brimonidine; Timolol	Yes	Yes	Multi (25)	United States	12	586	Intention-to-treat

Legend:
1. * Only showing drugs eligible for our systematic review
2. NA: not applicable
3. NR: not report
4. IOP: intraocular pressure

Table 3.3. Characteristics of included trials (trials from ClinicalTrials.gov)

ClinicalTrials.gov identifier	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared *	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up, months	Number of participants or eyes included	Types of analysis
NCT00277498	2007	Included	Included	NA	Excluded	NA	NR	>=18	NA	Excluded	NA	Latanoprost; Timolol	Yes	No	Multi (64)	United States	3	528	NR
NCT00332384	2001	Included	Included	NA	Can't tell	Can't tell	Inclusion criteria: patient requires IOP-lowering drug in both eyes	>=18	NA	NA	NA	brimonidine/timolol fixed combination	Can't tell	No	Single	United States	NR	573	NR
NCT00332436	2001	Included	Included	NA	Can't tell	Can't tell	Inclusion criteria: patient requires IOP-lowering drug in both eyes	>=18	NA	NA	NA	brimonidine/timolol fixed combination	Can't tell	No	Single	United States	NR	586	NR
NCT00539526	2008	Included	Included	NA	NA	Included	NR	>=18	NA	NA	NA	Bimatoprost; Travoprost; Latanoprost	Can't tell	No	Can't tell	United States	3	106	NR
NCT00690794	2009	Included	Included	NA	NA	NA	Intraocular pressure (IOP) controlled with latanoprost 0.005% (XALATAN®) for at least one continuous month prior to Visit 1.	>=18	NA	NA	NA	Travoprost; Latanoprost	Yes	No	Multi (70)	United States	3	726	Intention-to-treat
NCT00705757	2011	Included	Included	NA	NA	NA	NR	>=30	NA	NA	NA	Bimatoprost; Travoprost; Latanoprost	No	No	Multi (2)	United States	12	89	NR
NCT00708422	2009	Included	Included	NA	NA	NA	IOP controllable and stable on the study medication alone (both eyes).	>=18	Excluded	Excluded	Excluded	Travoprost; Latanoprost	Yes	No	Multi (21)	United States	3	231	Intention-to-treat
NCT00751049	1993	Included	Included	NA	Excluded	Included	IOP of 22mmHg or higher obtained	>=40	Excluded	Excluded	Excluded	Latanoprost; Timolol	Yes	Yes	Multi (12)	United Kingdom	6	294	NR

ClinicalTrials.gov identifier	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared *	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up, months	Number of participants or eyes included	Types of analysis
							during the pre-study period.												
NCT00751062	1993	Included	Included	NA	Excluded	Included	IOP of 22mmHg or higher obtained during the pre-study period.	>=40	Excluded	Excluded	Excluded	Latanoprost; Timolol	Can't tell	No	Multi (13)	Denmark; Finland; Norway; Sweden	6	267	NR
NCT00751127	1994	Included	Included	NA	Excluded	Included	IOP of 22mmHg or higher obtained during the pre-study period.	>=40	Excluded	Excluded	Excluded	Latanoprost; Timolol	Yes	Yes	Multi (17)	United States	6	268	NR
NCT00761319	2009	Included	Included	NA	NA	NA	NR	>=18	NA	NA	NA	Travoprost; Latanoprost	Yes	No	Multi (78)	United States	3	705	Intention-to-treat
NCT00763061	2008	Included	Included	NA	NA	Can't tell	IOP=16-30mmHg	>=18	Excluded	NA	Excluded	Travoprost; Timolol	No	Yes	Multi (4)	United States	3	111	NR
NCT00798759	2009	Included	Included	NA	NA	NA	NR	>=18	Can't tell	Excluded	Can't tell	Travoprost; Latanoprost	Yes	No	Multi (22)	United States	3	236	Intention-to-treat
NCT00961649	2010	Included	Included	Excluded	Excluded	Can't tell	Mean intraocular pressure within protocol-specified range at eligibility visit/s.	>=18	Excluded	Excluded	Excluded	Brinzolamide; Brimonidine	Yes	Yes	Multi (9)	United States	1.5	170	Intention-to-treat; Per protocol; Safety population or safety analysis
NCT00991822	2001	Included	Included	NA	Excluded	Excluded	IOP higher than 22 mmHg in at least one eye	>=19	Excluded	Excluded	Excluded	Dorzolamide; Timolol	Yes	Yes	Single	Austria	3	160	NR
NCT01001195	2010	Included	Included	Can't tell	Can't tell	NA	NR	>=18	Excluded	NA	Excluded	Bimatoprost	No	No	Can't tell	United States	1	165	Modified intention-to-treat; Safety population or safety analysis

ClinicalTrials.gov identifier	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared *	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of follow up, months	Number of participants or eyes included	Types of analysis
NCT01026831	2010	Included	Included	NA	NA	Included	Inclusion criteria: a mean (or median) IOP of >=23 and =<36 in at least one eye at the 08:00 hour time point at the Baseline Visit. Patient has <5 mmHg difference in mean (or median) IOP between eyes at each time point (0800 hours, 1000 hours, and 1600 hours) at Baseline. Exclusion Criteria: Patient has a mean (or median) IOP >36 mmHg in either eye at the Screening Visit or at any time point (0800 hours, 1000 hours, and 1600 hours) of the Baseline Visit.	>=18	Excluded	NA	Excluded	Tafluprost; Timolol	Yes	Yes	Can't tell	NR	3	643	Per protocol
NCT01110499	2011	Included	Included	Excluded	Excluded	Excluded	NR	>=18	NA	NA	NA	Bimatoprost	Can't tell	No	Can't tell	United States	1	163	Modified intention-to-treat
NCT01155219	2009	Included	Included	NA	Excluded	Excluded	NR	>=18 & <=90	NA	NA	NA	Latanoprost; Timolol	Yes	No	Can't tell	France	3	150	"Full analysis set"
NCT01223378	2011	Included	Included	NA	Excluded	NA	NR	>=18	NA	NA	NA	Latanoprost	Can't tell	No	Multi (NR)	United States	1	355	NR
NCT01253902	2011	Included	Included	NA	NA	NA	NR	>=18	Excluded	Excluded	Excluded	Bimatoprost; Travoprost; Latanoprost	Can't tell	No	Multi (NR)	United States; Canada	3	164	Intention-to-treat

ClinicalTrials.gov identifier	Year	Primary open angle glaucoma (POAG)	Ocular hypertension (OHT) or glaucoma suspect	Normal/low tension glaucoma	Angle closure glaucoma	Secondary glaucoma	IOP	Age, years	Prior glaucoma surgery	Prior glaucoma laser	Prior cataract surgery	Drugs compared *	Allowed ocular hypotensive medication at enrollment	Reported using a washout period before randomization	Multi/single center trial (# of recruiting centers)	Countries in which participants were recruited	Maximal planned length of followup, months	Number of participants or eyes included	Types of analysis
NCT01254604	2013	Included	Included	NA	NA	Included	Exclusion criteria: Mean IOP >36 mmHg in either eye at screening.	>=18 & <=80	Excluded	NA	Excluded	Tafluprost; Timolol	Yes	Yes	Can't tell	NR	1	190	Per protocol; "All patients as treated"
NCT01297517	2012	Included	Included	Excluded	Excluded	Can't tell	mean intraocular pressure within protocol-specified range at eligibility visit/s.	>=18	Excluded	Excluded	Excluded	Brinzolamide; Brimonidine	Yes	Yes	Multi (68)	United States	3	1001	Intention-to-treat
NCT01297920	2012	Included	Included	Excluded	Excluded	Can't tell	mean intraocular pressure within protocol-specified range at eligibility visit/s.	>=18	Excluded	Excluded	NA	Brinzolamide; Brimonidine	Yes	Yes	Multi (64)	United States	3	1062	Intention-to-treat
NCT01310777	2013	Included	Included	Can't tell	Can't tell	Can't tell	Meet qualifying IOP entry criteria.	>=18	Excluded	Excluded	Excluded	Brinzolamide; Brimonidine	Yes	Yes	Multi (63)	NR	6	771	Intention-to-treat
NCT01664039	2014	Included	Included	NA	NA	NA	Intraocular pressure (IOP) between 19 mmHg and 35 mmHg in at least one eye, which would be the study eye.	>=18	Excluded	Excluded	Excluded	Bimatoprost; Travoprost	No	No	Multi (2)	Slovenia	6	104	Modified intention-to-treat
NCT02140060	2014	Included	Included	Can't tell	Can't tell	Included	IOP within the protocol-specified range at both the Eligibility 1 and 2 Visits. Mean IOP must not be >36 mmHg at any time point.	>=18	Excluded	Excluded	Excluded	Travoprost; Brinzolamide	Yes	Yes	Multi (19)	United States	1.5	327	Modified intention-to-treat

Legend:
1. * Only showing drugs eligible for our systematic review
2. NA: not applicable
3. NR: not report
4. IOP: intraocular pressure

Table 4.1. Risk of bias assessment (trials from bibliographic databases)

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
1	NR	NR	NR	NR	Yes	Yes
2	Randomly numbered with a unique code by a third party	Each patient, in sequence, was assigned a study number corresponding to a test drug. The code was broken at the end of the study.	Yes	Yes	No	NR
3	NR	NR	NR	NR	Yes	Yes
4	NR	NR	NR	NR	Yes	NR
5	NR	NR	NR	NR	Yes	NR
6	NR	NR	NR	NR	Yes	NR
7	NR	NR	Yes	NR	Yes	NR
8	NR	NR	Yes	NR	Yes	Yes
9	NR	NR	NR	NR	Yes	NR
10	NR	Patients were then randomly assigned in a double-masked fashion to one of two treatment groups.	NR	NR	Yes	Yes
11	NR	NR	Yes	NR	Yes	NR
12	NR	NR	NR	NR	Yes	NR
13	NR	NR	Yes	Yes	No	NR
14	The treatment assignment was done in stratified groups based on the patient's baseline IOP and the number of eyes which were entered in the study.	The randomization list was kept by the research secretary, and the examining physician did not know to which group a newly recruited patient would be assigned.	No	Yes	No	Yes
15	NR	NR	NR	NR	Yes	Yes
16	NR	The randomization list was kept by each controller until the end of the study.	NR	NR	Yes	NR
17	NR	NR	No	NR	No	Yes
18	NR	NR	Yes	NR	Yes	NR
19	NR	NR	Yes	NR	No	NR
20	Participating patients were distributed randomly, i.e. each new patient entering the study received the next-numbered, masked bottle.	Participating patients were distributed randomly, i.e. each new patient entering the study received the next-numbered, masked bottle.	NR	NR	Yes	Yes
21	The containers were confirmed as indistinguishable, and allotted in a randomized manner by the controller. The key code table was retained by the controller.	The containers were confirmed as indistinguishable, and allotted in a randomized manner by the controller. The key code table was retained by the controller.	Yes	NR	Yes	NR

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
22	NR	NR	Yes	NR	Yes	Yes
23	NR	NR	NR	NR	Yes	NR
24	NR	NR	NR	NR	Yes	Yes
25	NR	NR	No	NR	No	NR
26	NR	NR	NR	NR	No	NR
27	The patients were allocated to treatment groups according to a computer-generated scheme prepared by Pharmacia.	NR	Yes	NR	Yes	Yes
28	Subjects were then placed on either placebo or timolol drops in both eyes twice a day in a double masked manner using randomized number tables.	NR	Yes	Yes	No	Yes
29	NR	NR	Yes	NR	Yes	Yes
30	NR	NR	NR	NR	Yes	Yes
31	NR	NR	Yes	NR	Yes	NR
32	NR	NR	Yes	NR	Yes	NR
33	NR	NR	NR	NR	Yes	NR
34	NR	NR	Yes	NR	Yes	Yes
35	The patients were allocated to different treatment groups according to a pregenerated randomization list.	NR	NR	NR	Yes	Yes
36	Envelope method	Envelope method	NR	NR	No	NR
37	NR	NR	NR	NR	Yes	NR
38	NR	NR	NR	NR	Yes	Yes
39	The randomization was stratified for center and performed in blocks of six consecutive patients within each center.	NR	NR	NR	Yes	NR
40	Patients with an IOP of greater than or equal to 24 mm Hg in at least one eye (the same eye) at hours 0 and 2 were then randomly assigned, according to a computer-generated allocation schedule.	NR	Yes	NR	Yes	NR
41	The patients were allocated to the treatment groups according to a computer-generated list prepared by Pharmacia & Upjohn (Uppsala, Sweden).	NR	NR	NR	Yes	Yes

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
42	Randomization schedules were generated for each site using SAS (Version 6.08; SAS Institute, Cary, NC) procedure, PROC PLAN.	Patients were assigned sequentially to masked treatment according to a randomization schedule generated by the study sponsor (Allergan, Inc). Each bottle of test medication was coded with a shipment number and labeled with a study number. Each time a bottle was dispensed to a patient, the tearoff portion of the label was attached to the patient's case-report form.	Yes	Yes	No	Yes
43	NR	NR	Yes	NR	Yes	Yes
44	Computer-generated randomization code	All clinical supplies were labeled based on a computer-generated randomization code and dispensed in numerical sequence to patients at each investigational site.	Yes	NR	Yes	Yes
45	Patients randomly (according to a computer-generated allocation schedule) received one of the following masked treatment regimens for 3 months	All study medication was packaged in identical bottles by allocation number	Yes	NR	Yes	Yes
46	NR	NR	No	Yes	No	NR
47	NR	NR	NR	NR	Yes	Yes
48	NR	NR	NR	NR	Yes	NR
49	NR	NR	No	No	Yes	Yes
50	NR	NR	No	No	No	Yes
51	NR	NR	Yes	NR	Yes	Yes
52	NR	NR	Yes	NR	Yes	Yes
53	Patients were randomized using computer-generated numbers (0 = receive latanoprost in the right eye and unoprostone in the left eye, 1 = receive unoprostone in the right eye and latanoprost in the left eye).	NR	No	Yes	No	NR
54	Patients were dispensed study medication that was packaged in identical bottles according to a computer-generated randomization list provided by	Patients were dispensed study medication that was packaged in identical bottles according to a computer-generated randomization list provided by Pharmacia & Upjohn, Sweden. Disclosure envelopes	Yes	NR	Yes	Yes

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
	Pharmacia & Upjohn, Sweden.	were kept in a locked cabinet at the study site. In the event of an emergency requiring identification of the masked treatment, the envelope could be opened. No envelopes were opened during the trial.				
55	The randomization schedule was generated using an SAS version 6.12 (SAS Inc., Cary, NC) program and stored in a locked cabinet.	The treatment identity was not revealed at any investigational site.	Yes	Yes	No	Yes
56	The Alcon Biostatistics Department prepared the computer-generated randomization schedule.	All patients received two identical DROPTAINER bottles labeled with a patient number and "morning" or "evening" according to the computer-generated randomization schedule provided by the Biostatistics Department at Alcon Laboratories	Yes	NR	Yes	Yes
57	Patients who met the eligibility criteria were then randomized, by a computer-generated schedule.	NR	Yes	NR	Yes	Yes
58	On the baseline day, the patients were randomized (by block randomization) to two parallel study groups.	NR	No	Yes	No	No
59	The method used for preparing the allocation schedule was based on blocked randomization, in blocks of eight allocation numbers.	Patients were assigned allocation numbers at the prestudy visit. Drops were contained in identical bottles marked with allocation numbers. During the study the assignment codes were kept in sealed envelopes in a locked space at the study location, and were delivered with unbroken seals on completion of trial.	Yes	Yes	No	Yes
60	Patients who met all study eligibility criteria were assigned a patient number and	Medication description was concealed from the patient, investigator, and clinical study staff.	Yes	Yes	No	Yes

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
	sequentially randomly assigned to one of three treatment groups in an equal (1:1:1) ratio by means of a computer generated randomization schedule prepared by the Alcon Biostatistics Department. Randomization was stratified by site to ensure balanced treatment within each site.	Masked medication was packaged in identical Drop-Tainers and provided to the investigators along with sealed envelopes containing the medication description for each patient.				
61	Patients were allocated to 1 of 3 treatment groups according to a computer-generated randomization code list. A single block randomization list was generated for the entire study.	Drug was issued according to patient numbers that were given in consecutive order at baseline. Medications were provided in identical coded bottles. Study medication was shipped to the individual study sties in sets such that each set was a multiple of the block size used in generating the randomization.	NR	NR	Yes	Yes
62	Randomization codes were generated and medical supplies were prepared by Pharmacia clinical Supply Logistics (Kalamazoo, Michigan, USA).	Each center received prepackaged clinical supplies with patient numbers, which were allocated sequentially.	No	NR	No	Yes
63	NR	NR	NR	NR	Yes	Yes
64	Computer-generated randomization schedule	Medication identity was concealed in individually sealed envelopes stored at the study sites.	Yes	NR	Yes	Yes
65	NR	NR	Yes	NR	Yes	Yes
66	the randomization code was maintained at the central coordination center.	NR	Yes	NR	Yes	Yes
67	NR	NR	No	NR	Yes	Yes
68	The Central Registration System controller randomly allocated patients into these two groups by assigning patients into blocks in sequence of registration to the center, which was determined by the investigators. Each block consisted of six	The Central Registration System controller randomly allocated patients into these two groups by assigning patients into blocks in sequence of registration to the center, which was determined by the investigators. Each block consisted of six patients for a set of treatments	NR	NR	No	NR

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
	patients for a set of treatments (three latanoprost, three unoprostone) where the order of treatments within the block had been randomized.	(three latanoprost, three unoprostone) where the order of treatments within the block had been randomized.				
69	NR	NR	NR	NR	Yes	Yes
70	NR	NR	Yes	Yes	Yes	Yes
71	NR	NR	No	No	No	NR
72	The chief pharmacist at Moorfields Eye Hospital, who had no other direct involvement with the trial, randomised one of the patients in each pair to treatment with either betaxolol drops or placebo drops. The fellow member of the pair was then allocated to the alternative treatment arm. Randomisation was carried out by means of randomisation tables.	Each patient was assigned drops coded either A, B, C or D that corresponded to their trial number.	Yes	Yes	No	Yes
73	NR	NR	No	Yes	No	Yes
74	The randomization schedule was generated using the SAS (version 6.12) procedure PROC PLAN and the printout was stored in a locked cabinet.	NR	Yes	Yes	No	Yes
75	NR	NR	No	Yes	Yes	NR
76	NR	NR	NR	NR	No	NR
77	At the baseline visit (day 0), eligible patients were randomly assigned, using a computer-generated randomization code list, to 1 of 2 treatment groups.	NR	No	No	No	NR
78	The randomization schedule was generated using a SAS (version 6.12) program and stored in a locked cabinet until the study was completed.	The randomization schedule was generated using a SAS (version 6.12) program and stored in a locked cabinet until the study was completed.	No	No	Yes	Yes
79	A computer-generated list of random assignments decided	The list was sealed and could be opened only after the completion of	NR	NR	Yes	NR

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
	which treatment patients would receive.	the study protocol or after any serious adverse event occurred.				
80	Computer generated	Assign patient numbers sequentially; opaque syndiotactic polypropylene oval bottles.	Yes	NR	Yes	Yes
81	Randomization was performed by centralized allocation by Voice Processing Plus, Inc., via an interactive phone registration system.	Randomization was performed by centralized allocation by Voice Processing Plus, Inc., via an interactive phone registration system.	NR	Yes	No	Yes
82	Randomization was obtained at the Coordinating Center. Each clinical center had its own randomization list that was stratified for pseudoexfoliation, pigmentary dispersion syndrome, and diabetes mellitus.	Bottles of drug and placebo were given to each center according to the randomization list. Patients were given a bottle marked with a code label. The allocation code was secured at the Coordinating Center at the office of the Project Coordinator.	Yes	Yes	No	Yes
83	NR	NR	NR	NR	Yes	NR
84	The randomization sequence was generated by the study sponsor using the PLAN procedure in SAS version 6.12 (SAS Institute Inc, Cary, NC).	Before initiation of study treatment, each patient who qualified for entry was assigned a patient randomization number, which was used on all documentation.	Yes	NR	Yes	Yes
85	NR	NR	NR	Yes	Yes	NR
86	NR	NR	NR	Yes	No	No
87	Randomization was achieved by asking the participants to choose any number between 1 and 10; even and odd numbers were assigned to bimatoprost (n=41) and travoprost (n=49) groups, respectively.	NR	NR	Yes	No	NR
88	Patients were randomized in a ratio of 2:1:1 to the FC (q.d., mornings), BIM 0.03% (q.d., evenings), or TIM 0.5% (b.i.d.) using a computer- generated randomization list (PROC PLAN, SAS	NR	NR	NR	Yes	Yes

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
	Ver- sion 8.2, Cary, NC).					
89	NR	White plastic dropper bottles, each labeled with a unique patient number.	Yes	NR	Yes	Yes
90	NR	NR	Yes	NR	Yes	Yes
91	A list of random numbers	Standard containers were used and they were concealed with a study-specific cover and all kept in a standard opaque black medicine vial	Yes	NR	Yes	NR
92	Randomization lists were used to preallocate treatment kits to each patient number by personnel not involved with the management of the study.	Randomization lists were used to preallocate treatment kits to each patient number by personnel not involved with the management of the study.	No	No	No	Yes
93	Allocation was based on computer-generated random numbers and was concealed by using sequentially numbered opaque sealed envelopes.	Allocation was based on computer-generated random numbers and was concealed by using sequentially numbered opaque sealed envelopes.	NR	NR	No	NR
94	Fifty opaque envelopes containing random numbers (drugs in code forms), generated with the help of table of randomization, were prepared in advance by an investigator who was not related to the study. Whenever, a study participant was found to be eligible, an envelope was opened by another person in the department and the patient was put on the allocation plan as found inside the envelope in coded form.	Fifty opaque envelopes containing random numbers (drugs in code forms), generated with the help of table of randomization, were prepared in advance by an investigator who was not related to the study. Whenever, a study participant was found to be eligible, an envelope was opened by another person in the department and the patient was put on the allocation plan as found inside the envelope in coded form.	Yes	No	No	NR
95	NR	NR	NR	NR	No	NR
96	These kit numbers had been randomized by the study sponsor using statistical software (SAS Institute, Cary, NC).	At the study site, the enrolling clinician assigned a number to the patient, and then called an interactive voice response system that was hosted by the study sponsor in order to receive a kit number.	Yes	NR	Yes	Yes

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
97	A randomization schedule, balanced for ethnicity and drug assignment, was produced for each participating site by the biostatistician.	NR	No	Yes	No	No
98	The randomization sequence was computer-generated.	the randomization code was retained by the study sponsor and made available to the investigators only after the study had ended.	Yes	No	Yes	Yes
99	Randomization codes were generated by Pfizer according to standard operating procedures and were kept at Global Pharmacy Operations (New York, New York).	NR	NR	Yes	No	Yes
100	The randomisation code was computer-generated.	NR	No	NR	Yes	Yes
101	NR	NR	NR	NR	No	No
102	Patients were randomized using Proc Plan, SAS for Windows (version 8.2; SAS Institute Inc., Cary, NC).	NR	Yes	NR	Yes	Yes
103	NR	patients were provided with identically appearing sealed cartons, labeled with the patient randomization number, which contained marketed bottles of the study medications, and patients were instructed not to disclose their study medication to the investigator or office personnel.	No	Yes	No	Yes
104	NR	NR	NR	NR	Yes	Yes
105	NR	NR	No	No	No	No
106	NR	NR	No	No	Yes	NR
107	Randomization was performed by Ms. Takako Komiya... in research center, after confirming identical appearance of both treatments.	Randomization was performed by Ms. Takako Komiya... in research center, after confirming identical appearance of both treatments.	NR	NR	Yes	Yes
108	Patients were assigned to treatment using a computer-generated	Personnel at each study site used an interactive voice response system to	Yes	Yes	No	Yes

Reference ID¶	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
	randomized allocation schedule prepared by a statistician at Merck	determine which masked treatment containers should be given to which patient.				
109	NR	NR	No	NR	Yes	Yes
110	NR	NR	No	No	No	NR
111	A list of sequential patient numbers was generated by a member of the sponsor programming group (SAS Institute) not involved in the conduct of the study.	A list of sequential patient numbers was generated by a member of the sponsor programming group (SAS Institute) not involved in the conduct of the study. Study medications were provided in identical bottles. Staff members who provided the study medications to patients did not discuss those medications with other site personnel.	Yes	NR	No	Yes
112	NR	NR	NR	NR	Yes	Yes
113	NR	A designee at each study site, other than the investigator, was responsible for the dispensing study treatment	No	Yes	No	Yes
114	Subjects received masked kits for 2 weeks of study medication via an interactive voice response system using a computer-generated random allocation schedule.	Subjects received masked kits for 2 weeks of study medication via an interactive voice response system using a computer-generated random allocation schedule.	Yes	NR	Yes	Yes

Legend:
1. ¶ See Appendix 2 for reference ID
2. NR: not report
3. IOP: intraocular pressure
4. Color coding:

Green	Low risk of bias
Yellow	Unclear risk of bias
Red	High risk of bias

Table 4.2. Risk of bias assessment (trials from Drugs@FDA)

Druas@FDA NDA-Protocol Number	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
204251 C-09-038	NR	NR	Yes	NR	Yes	Yes
204251 C-10-033	NR	NR	NR	NR	Yes	Yes
204251 C-10-039	NR	NR	NR	NR	Yes	Yes
20816 C-95-46	NR	NR	NR	NR	Yes	Yes
20816 C-95-48	NR	NR	NR	NR	Yes	Yes
20869 44	NR	NR	NR	NR	Yes	Yes
20869 47	NR	NR	NR	NR	Yes	Yes
20869 63	NR	NR	NR	NR	Yes	Yes
20869 64	NR	NR	NR	NR	Yes	Yes
21114 C-97-40	NR	NR	Yes	NR	Yes	Yes
21114 C-97-67	NR	NR	Yes	NR	Yes	Yes
21114 C-97-80	NR	NR	Yes	NR	Yes	Yes
21214 C97-UIOS-004	NR	NR	Yes	NR	Yes	Yes
21214 C97-UIOS-005	NR	NR	Yes	NR	Yes	Yes
21214 C97-UIOS-003	NR	NR	Yes	NR	Yes	Yes
21257 C-97-71	NR	NR	Yes	NR	Yes	Yes
21257 C-97-72	NR	NR	Yes	NR	Yes	Yes
21257 C-97-79	NR	NR	Yes	NR	Yes	Yes
21257 C-97-02	NR	NR	Yes	NR	Yes	Yes
21257 C-97-73	NR	NR	NR	NR	Yes	Yes
21262 190342-005	They [the investigational materials] were coded at Allergan using a computer-generated randomization list.	NR	NR	NR	Yes	Yes
21275 192024-008	NR	NR	NR	NR	Yes	Yes
21275 192024-009	NR	NR	NR	NR	Yes	Yes
21275 192024-002	NR	NR	No	NR	Yes	Yes
21275 192024-003	NR	NR	Yes	NR	Yes	Yes
21275 192024-004	NR	NR	No	NR	Yes	Yes
21398 190342-012T	NR	Each identically masked bottle of test medication was labeled with a patient number.	Yes	No	Yes	Yes
21398 190342-013T	NR	Each identically masked bottle of test medication was labeled with a patient number.	Yes	No	Yes	Yes

Legend:
1. NR: not report
2. IOP: intraocular pressure
3. Color coding:

Green	Low risk of bias
Yellow	Unclear risk of bias
Red	High risk of bias

Table 4.3. Risk of bias assessment (trials from ClinicalTrials.gov)

ClincalTrials.gov identifier	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry
NCT00277498	NR	NR	NR	NR	Yes	Yes
NCT00332384	NR	NR	NR	NR	Yes	Yes
NCT00332436	NR	NR	NR	NR	Yes	Yes
NCT00539526	NR	NR	No	NR	Yes	Yes
NCT00690794	NR	NR	Yes	NR	Yes	Yes
NCT00705757	NR	NR	No	NR	No	No
NCT00708422	NR	NR	Yes	NR	Yes	Yes
NCT00751049	NR	NR	Yes	NR	Yes	Yes
NCT00751062	NR	NR	Yes	NR	Yes	Yes
NCT00751127	NR	NR	Yes	NR	Yes	Yes
NCT00761319	NR	NR	Yes	NR	Yes	Yes
NCT00763061	NR	NR	Yes	NR	Yes	Yes
NCT00798759	NR	NR	Yes	NR	Yes	Yes
NCT00961649	NR	NR	Yes	Yes	No	Yes
NCT00991822	NR	NR	No	NR	Yes	No
NCT01001195	NR	NR	No	Yes	Yes	Yes
NCT01026831	NR	NR	Yes	NR	Yes	Yes
NCT01110499	NR	NR	Yes	NR	Yes	Yes
NCT01155219	NR	NR	No	No	No	Yes
NCT01223378	NR	NR	No	NR	Yes	Yes
NCT01253902	NR	NR	No	NR	Yes	Yes
NCT01254604	NR	NR	Yes	NR	Yes	Yes
NCT01297517	NR	NR	Yes	Yes	Yes	Yes
NCT01297920	NR	NR	Yes	Yes	Yes	Yes
NCT01310777	NR	NR	Yes	Yes	Yes	Yes
NCT01664039	NR	NR	No	Yes	No	Yes
NCT02140060	NR	NR	Yes	NR	Yes	Yes

Legend:
1. NR: not report
2. IOP: intraocular pressure
3. Color coding:

Green	Low risk of bias
Yellow	Unclear risk of bias
Red	High risk of bias

Table 5. Comparison of reporting of trials (bibliographic databases vs Drugs@FDA vs ClinicalTrials.gov) Part1

No.	Clinical Trials.gov identifier	Reference ID¶	Drugs@FDA NDA-Protocol number	Eligibility criteria		Region or country of recruitment	Maximum length of follow-up after randomization		Sample size calculation	Types of analysis described		Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study	Number of study groups		Treatments compared		Sample size at baseline	Age	Sex	Availability of outcome data			
																								IOP	Visual field	Vertical cup/disc ratio	Central visual acuity
1	NCT01297517	111	204251(c-10-033)	J	F				J	E			J	J	C				M		M	M	M				
2	NCT01297920	112	204251(c-10-039)	J	F				J	F		C			C				F	C	M	M	M				
3	NCT00332436	84	21398(190342-013T)	F			J	F	J	J	F	J	J	J			J	F	Non-comparable					J	F	F	F
4	NCT00332384		21398(190342-012T)	F			J	F	J	J	F	J	J	J			J	F						J	F	F	F

Table 5. Comparison of reporting of trials (bibliographic databases vs Drugs@FDA vs ClinicalTrials.gov) Part1 details

No.	ClinicalTrials.gov identifier	Reference ID¶	Drugs@FDA NDA-Protocol number	Eligibility criteria		Region or country of recruitment	Maximum length of follow-up after randomization		Sample size calculation	Types of analysis described		Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
1	NCT01297517	111	204251(c-10-033)	B1b-B1m. Inclusion criteria. IOP requirement specification. Journal article: reported. ClinicalTrials.gov: NR	B1b-B1m. Inclusion criteria. IOP requirement specification. FDA: reported. ClinicalTrials.gov: NR.				Power calculation. Journal article: Reported. FDA and ClinicalTrials.gov: NR	Journal article: intention-to-treat, "Safety population" or "Safety analysis". FDA: intention-to-treat, per protocol. ClinicalTrials.gov: intention-to-treat			Journal article: reported. FDA and ClinicalTrials.gov: NR	Journal article: reported. FDA and ClinicalTrials.gov: NR	ClinicalTrials.gov: reported. Journal article and FDA:NR	
2	NCT01297920	112	204251(c-10-039)	B1b-B1m. Inclusion criteria. IOP requirement specification. Journal article: reported. ClinicalTrials.gov: NR	B1b-B1m. Inclusion criteria. IOP requirement specification. FDA reported. ClinicalTrials.gov: NR.				Power calculation. Journal article: Reported. FDA and ClinicalTrials.gov: NR	FDA: intention-to-treat, per protocol. "Safety population" or "Safety analysis" Journal article and ClinicalTrials.gov: intention-to-treat, "Safety population" or "Safety analysis"		ClinicalTrials.gov: reported. Journal article and FDA:NR.			ClinicalTrials.gov: reported. Journal article and FDA:NR	
3	NCT00332436	84	21398(190342-013T)	B1b-B1m. 1) Inclusion criteria .Secondary glaucoma. FDA: yes. Journal article and ClinicalTrials.gov: can't tell. IOP requirement. Journal article and FDA: reported. ClinicalTrials.gov: NR. 2) Exclusion criteria. Journal article and FDA: ocular surgery within the past 3			Journal article: reported. ClinicalTrials.gov: NR	FDA: reported. ClinicalTrials.gov: NR	Power calculation. Journal article: Reported. FDA and ClinicalTrials.gov: NR	Journal article: ITT. ClinicalTrials.gov: NR	FDA: ITT. ClinicalTrials.gov: NR	Journal article: reported. FDA and ClinicalTrials.gov: NR	Journal article: reported. FDA and ClinicalTrials.gov: NR	Journal article: reported. FDA and ClinicalTrials.gov: NR		
4	NCT00332384		21398(190342-012T)													

No.	ClinicalTrials.gov identifier	Reference ID¶	Drugs @FDA NDA-Protocol number	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization		Sample size calculation	Types of analysis described		Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
				months. ClinicalTrials.gov: NR											

Table 5. Comparison of reporting of trials (bibliographic databases vs Drugs@FDA vs ClinicalTrials.gov) Part1 details (continued)

No.	ClinicalTrials.gov identifier	Reference ID¶	Drugs@FDA NDA-Protocol number	Number of study groups		Treatments compared		Sample size at baseline	Age	Sex	Availability of outcome data				
											IOP		Visual field	Vertical cup/disc ratio	Central visual acuity
1	NCT01297517	111	204251(c-10-033)			E2. Number of participants randomized. Journal article: 216:225:219. FDA: 216:225:219. ClinicalTrials.gov: 214:226:220		Journal article and FDA: 209:224:216. ClinicalTrials.gov: 214:226:220	Age<65. Publication and FDA: 104:99:115. ClinicalTrials.gov: 107:101:117	Female. Journal article and FDA: 136:127:132. ClinicalTrials.gov: 140:128:135.					
2	NCT01297920	112	204251(c-10-039)			E2. Number of participants randomized in each group. FDA: reported. Journal article:NR	E2. Number of participants randomized in each group. ClinicalTrials.gov: reported. Journal article:NR	Journal article and FDA: 218:229:232. ClinicalTrials.gov: 221:234:235	Age<65. Publication and FDA: 98:110:115. ClinicalTrials.gov: 99:113:115	Female. Journal article and FDA: 118:132:131. ClinicalTrials.gov:119: 136:132					
3	NCT00332436	84	21398(190342-013T)	Journal article: reported. ClinicalTrials.gov: NR	FDA: reported. ClinicalTrials.gov: NR	Journal article: merged two trials. FDA: reported sepately. ClinicalTrials.gov: NR					Journal article: reported. ClinicalTrials.gov: NR	FDA: reported. ClinicalTrials.gov: NR	FDA: reported. Journal article and ClinicalTrials.gov: NR	FDA: reported. Journal article and ClinicalTrials.gov: NR	FDA: reported. Journal article and ClinicalTrials.gov: NR
4	NCT00332384		21398(190342-012T)												

Table 5. Comparison of reporting of trials (bibliographic databases vs Drugs@FDA vs ClinicalTrials.gov) Part 2

No.	ClinicalTrials.gov identifier	Reference ID ¶	Drugs@FDA NDA-Protocol number	Source	Primary outcomes	Other outcomes				Primary outcome				
						Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	Other outcomes (CT.gov)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
1	NCT01297517	111	204251(c-10-033)	Journal article	Mean IOP at the 3-month visit at all 4 time points.	1. The mean IOP at the 2-week and 6-week visits for all time points. 2. AEs, CDVA, slitlamp biomi-croscopy observations, pachymetry, automated perimetry, fun-dus variables, and resting pulse rate and blood pressure.	**1. Baseline mean IOP levels at each of the 4 time points.** **2. percentage reduction in IOP from baseline to the 3-month visit.** 3. AEs, CDVA, slitlamp biomicroscopy observations, pachymetry, automated perimetry, fundus variables, and resting pulse rate and blood pressure.			Goldmann applanation tonometer.	8AM, 10AM, 3PM, 5PM	IOP	Mean	Results slightly differ among three sources
				FDA approval packages				1. Mean IOP at baseline, week 2, 6, and 12 visit at each of the 4 time points. 2. Mean IOP change from baseline at at baseline, week 2, 6, and 12 visit at each of the 4 time points. 3. AE and SAE. 4. Cardiovascular parameters		NR				

No.	ClinicalTrials.gov identifier	Reference ID ¶	Drugs @FDA NDA-Protocol number	Source	Primary outcomes	Other outcomes				Primary outcome				
						Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	Other outcomes (CT.gov)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
				ClinicalTrials.gov					1. AE and SAE.	Goldmann applanation tonometer.				
2	NCT01297920	112	204251(c-10-039)	Journal article		1.the mean IOP at the 2- and 6-week visits for all time points. 2. adverse events (AEs), BCVA, slit-lamp biomicroscopy observations, pachymetry, automated perimetry, fundus parameters, and resting pulse rate and blood pressure	1.the mean IOP at the 2- and 6-week visits for all time points. **2. % IOP reduction from baseline.** 3. adverse events (AEs), BCVA, slit-lamp biomicroscopy observations, pachymetry, automated perimetry, fundus parameters, and resting pulse rate and blood pressure			Goldmann applanation tonometer.	8AM, 10AM, 3PM, 5PM	IOP	Mean	Same
				FDA approval packages				1. Mean IOP at baseline, week 2, 6, and 12 visits at each of the 4 time points. 2. Mean IOP change from baseline at at baseline, week 2, 6, and 12 visits at each of the 4 time points. 3. AE and SAE. 4. Cardiovascular parameters		NR				

No.	ClinicalTrials.gov identifier	Reference ID ¶	Drugs @FDA NDA-Protocol number	Source	Primary outcomes	Other outcomes				Primary outcome				
						Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	Other outcomes (CT.gov)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
				ClinicalTrials.gov	Mean IOP at the 3-month visit at each of the 4 time points.				1. AE and SAE.	Goldmann applanation tonometer.				
3	NCT00332436	84	21398(190342-013T)	Journal article	Mean change from baseline IOP at 8 AM, 10 AM, 3 PM, and 5 PM at weeks 2 and 6 and at months 3, 6, and 12.	1.Mean IOP. 2.The percentage of patients reaching a mean daytime IOP of less than 18 mm Hg at all follow-up visits 3.The percentage of patients with a mean follow-up IOP within (14, 14-17.5, and 17.5 mm Hg) 4.The percentage of patients achieving a mean daytime decrease from baseline IOP of greater than 20% 5.The safety evaluation included an assessment of reported adverse events, biomicroscopy, tests of visual acuity and visual fields, ophthalmoscopy, cup-disc ratio, heart rate, blood pressure, complete blood cell count, serum chemistry, and urinalysis.				Goldmann applanation tonometer.	8AM, 10 AM, 3 PM, and 5 PM at weeks 2 and 6 and at months 3, 6, and 12.	Change from baseline	Mean	NR
				FDA approval packages	Mean change from baseline IOP at 8 AM, 10 AM, 3 PM, and 5 PM at weeks 2 and 6 and at months 3, 6, and 12.			Visual field, vertical cup/disc ratio, central visual acuity.		NR	8AM, 10 AM, 3 PM, and 5 PM at weeks 2 and 6 and at months 3, 6, and 12.	Change from baseline	Mean	reported
				ClinicalTrials.gov	NR				NR	NR	NR	NR	NR	NR

No.	ClinicalTrials.gov identifier	Reference ID ¶	Drugs @FDA NDA-Protocol number	Source	Primary outcomes	Other outcomes				Primary outcome				
						Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	Other outcomes (CT.gov)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
4	NCT00332384		21398(190342-012T)	Journal article	Mean change from baseline IOP at 8 AM, 10 AM, 3 PM, and 5 PM at weeks 2 and 6 and at months 3, 6, and 12.	1.Mean IOP. 2.The percentage of patients reaching a mean daytime IOP of less than 18 mm Hg at all follow-up visits 3.The percentage of patients with a mean follow-up IOP within (14, 14-17.5, and 17.5 mm Hg) 4.The percentage of patients achieving a mean daytime decrease from baseline IOP of greater than 20% 5.The safety evaluation included an assessment of reported adverse events, biomicroscopy, tests of visual acuity and visual fields, ophthalmoscopy, cup-disc ratio, heart rate, blood pressure, complete blood cell count, serum chemistry, and urinalysis.			Goldmann applanation tonometer.	8AM, 10 AM, 3 PM, and 5 PM at weeks 2 and 6 and at months 3, 6, and 12.	Change from baseline	Mean	NR
				FDA approval packages	Mean change from baseline IOP at 8 AM, 10 AM, 3 PM, and 5 PM at weeks 2 and 6 and at months 3, 6, and 12.		Visual field, vertical cup/disc ratio, central visual acuity.		NR	8AM, 10 AM, 3 PM, and 5 PM at weeks 2 and 6 and at months 3, 6, and 12.	Change from baseline	Mean	reported
				ClinicalTrials.gov	NR			NR	NR	NR	NR	NR	NR

Legend:
1. ¶ See Appendix 2 for reference ID
2. ROB: risk of bias
3. IOP: intraocular pressure
4. Color coding:

M	Misleading
X	Substantive difference across reports
J	Difference in completeness across reports, the journal article provides more information

F	Difference in completeness across reports, the FDA approval package provides more information
C	Difference in completeness across reports, the ClinicalTrials.gov registration provides more information
E	Difference in completeness across reports, each provides some information
	No difference across reports

Table 6. Comparison of reporting of trials (bibliographic databases vs Drugs@FDA) Part 1

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study	Number of study groups	Treatments compared	Sample size at baseline	Age	Sex	Availability of outcome data			
																		IOP	Visual field	Vertical cup/disc ratio	Central visual acuity
1	20869 47	39	J			J	J		J			F		J		J					
2	20869 63	40	J			J	J		J	J				J		J					
3	21275 192024-008	74	F			J	F		J	J	J								F	F	F
4	21275 192024-009	51	F			J	F	J	J	J									F	F	F
5	20816 C-95-46	50	J											J					J	J	
6	20816 C-95-48	44	J						J	J				J	M	F					
7	21214 C97-UIOS-005	64			M	J			J	J						J			F	F	F
8	21257 C-97-71	56	F			J			J		J			J					F	F	F
9	21257 C-97-72	60	E			J			J		J								F	F	F
10	21257 C-97-79	54				J			J										F	F	F

Table 6. Comparison of reporting trials (bibliographic databases vs Drugs@FDA) Part 1 details

No.	Drugs@FDA NDA-Protocol number	Refrence ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
1	20869 47	39	Exclusion cirteria. Journal article: history or vevidence of acute or chronic angle closure glaucoma; history or evidence of intraocular surgery; previous exposure to the dorzolamide–timolol combination. FDA:NR.			Power calculation. Journal article: Reported. FDA: NR	Journal article: All-Patients Treat, Last Observation Carried Forward (APT-LOCF) and per protocol. FDA: APT-LOCF		Journal article: reported. FDA: NR			FDA: reported. Journal article: NR
2	20869 63	40	Inclusion criteria: Journal article: a 3-week run-in taking 0.5% timolol twice daily monotherapy (days -21 to -1) FDA: a 3-week run-in. Exclusion cirteria. Journal article: best-corrected visual acuity worse than 20/80 in both eyes, contraindication to the use of beta-blockers, history or evidence of acute or chronic angle-closure glaucoma, intraocular surgery or trauma less than 6 months from study start, laser			Power calculation. Journal article: Reported. FDA: NR	Journal article:1) All-Patients Treat, Last Observation Carried Forward (APT-LOCF) 2) per protocol.3)"Safety population" or "Safety analysis". FDA: APT-LOCF		Journal article: reported. FDA: NR	Journal article: reported. FDA: NR		

No.	Drugs@FDA NDA-Protocol number	Refrence ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
			surgery less than 3 months from study start, and concomitant medications known to affect IOP.FDA:NR.									
3	21275 192024-008	74	1)Inclusion criteria: FDA: chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma; Journal article: NR. 2) Exclusion criteria: FDA: Previous use of AGN 192024 or another Allergan ocular hypotensive lipid. Journal article: NR			Power calculation. Journal article: Reported. FDA: NR	Journal article: ITT and safety population; FDA: ITT, per protocol, and safety population		Journal article: reported. FDA: NR	Journal article: reported. FDA: NR	Journal article: yes; FDA: unclear	
4	21275 192024-009	51	Exclusion criteria: FDA: Previous use of AGN 192024 or another Allergan ocular hypotensive lipid; laser surgery within past 3 months. Journal article: NR			Power calculation. Journal article: Reported. FDA: NR	Journal article: ITT and safety population; FDA: ITT, per protocol, and safety population	Journal article: reported. FDA: NR	Journal article: reported. FDA: NR	Journal article: reported. FDA: NR		
5	20816 c-95-46	50	1)Inclusion criteria. Journal article: pseudoexfoliative or pigmentary glaucoma. FDA:NR. 2) Exclusion criteria: Journal article: had had intraocular									

No.	Drugs@FDA NDA-Protocol number	Refrence ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
			surgery within the past 12 months or laser surgery within the past 3 months; having had therapy with an investigational agent within the past 30 days. FDA: NR.									
6	20816 c-95-48	44	1)Inclusion criteria. Journal article: pseudoexfoliative or pigmentary glaucoma. FDA:NR. 2)Exclusion criteria: Journal article: had had intraocular surgery within the past 12 months or laser surgery within the past 3 months; having had therapy with an investigational agent within the past 30 days. FDA: NR.						Journal article: reported. FDA: NR	Journal article: reported. FDA: NR		
7	21214 C97-UIOS-005	64			Journal article: 6 month data, 24 month study. FDA: 6month data 12 month study	Power calculation. Journal article: Reported. FDA: NR			Journal article: reported. FDA: NR	Journal article: reported. FDA: NR		
8	21257 c-97-71	56	Exclusion criteria: FDA: 1) any form of glaucoma other than OAG with or without a pigment dispersion or pseudoexfoliation component or ocular hypertension; 2)			Power calculation. Journal article: Reported. FDA: NR			Journal article: reported. FDA: NR		Journal article: yes; FDA: unclear	

No.	Drugs@FDA NDA-Protocol number	Refrenc e ID¶	Eligibility criteria	Region or country of recruitmen t	Maximum length of follow-up after randomizatio n	Sample size calculatio n	Types of analysis described	Participant s flow diagram	Descriptio n of sequence generation	Description of allocation concealmen t	Maskin g of IOP assessor	Fundin g for the study
			Ocular laser surgery within the past three months. Journal article:NR.									
9	21257 c-97-72	60	1) Inclusion criteria: Journal article: 21 years of age or older. FDA: NR. 2)Exclusion criteria: FDA: any form of glaucoma other than OAG with or without a pigment dispersion or pseudoexfoliatio n component or ocular hypertension; ocular laser surgery within the past three months. Journal article: NR.			Power calculation. Journal article: Reported. FDA: NR			Journal article: reported. FDA: NR		Journal article: yes; FDA: unclear	
10	21257 c-97-79	54				Power calculation. Journal article: Reported. FDA: NR			Journal article: reported. FDA: NR			

Table 6. Comparison of trial reporting (bibliographic databases vs Drugs@FDA) Part 1 details (continued)

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Number of study groups	Treatments compared	Sample size at baseline	Age	Sex	Availability of outcome data			
								IOP	Visual field	Vertical cup/disc ratio	Central visual acuity
1	20869 47	39		Placebo usage Journal article: reported. FDA: NR		Journal article: mean(SD) for each group and total. FDA: mean(SD) for each group.					
2	20869 63	40		Placebo usage Journal article: reported. FDA: NR		Journal article: mean(SD) for each group and total. FDA: mean(SD) for each group.					
3	21275 192024-008	74							FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.
4	21275 192024-009	51							FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.
5	20816 c-95-46	50		Placebo usage Journal article: reported. FDA: NR					Journal article: reported. FDA: NR	Journal article: reported. FDA: NR	
6	20816 c-95-48	44		Number of participants randomized in this study. Journal article: reported. FDA: NR. Placebo usage Journal article: reported. FDA: NR	Journal article: used per protocol population for table 1. FDA: used so-called ITT (received at least one dose	Mean(SD) of age in each group. Journal article: NR. FDA: reported.					

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Number of study groups	Treatments compared	Sample size at baseline	Age	Sex	Availability of outcome data			
								IOP	Visual field	Vertical cup/disc ratio	Central visual acuity
					of test medica-tion) for table 1						
7	21214 C97-UIOS-005	64				Journal article: mean(SD) for each group and total. FDA: mean(SD) for each group.			FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.
8	21257 c-97-71	56							FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.
9	21257 c-97-72	60							FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.	FDA: reported. Journal article: NR.
10	21257 c-97-79	54							FDA: reported. Journal article: NR.	FDA: reported.Journal article: NR.	FDA: reported. Journal article: NR.

Table 6. Comparison of reporting of trials (bibliographic databases vs Drugs@FDA) Part 2

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Source	Primary outcomes	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
1	20869 47	39	Journal article	mean percent change in IOP from baseline at month 3, hour 0	1.The mean IOP at baseline, week 2, month 1, month 2, month 3 of hour 0 and hour 2. 2. The mean and percent of IOP change from baseline at each time point. 3.AE and SAE. 4. Visual acuity, visual field results, optic nerve cup-to-disc ratio, etc.			NR	at week 2, month 1, month 2, month 3 of hour 0 and hour 2	IOP change from baseline	Mean percentage	Same
			FDA approval package	Unclear			1.The mean IOP at baseline, week 2, month 1, month 2, month 3 of hour 0 and hour 2. 2. The mean and percent change of IOP reduction from baseline at each time point. 3. AE. 4. Visual acuity, visual field results, optic nerve cup-to-disc ratio, etc.	NR	at week 2, month 1, month 2, month 3 of hour 0 and hour 2	IOP change from baseline	Mean percentage	Same
2	20869 63	40	Journal article	mean percent change in IOP from baseline at month 3, hour 0	1.The mean IOP at baseline, week 2, month 1, month 2, month 3 of hour 0 and hour 2. 2. The percent mean IOP reduction from baseline at each time point. 3.AE and SAE. 4. Visual acuity, visual field results, optic nerve cup-to-disc ratio, etc.			NR	at week 2, month 1, month 2, month 3 of hour 0 and hour 2	IOP change from baseline	Mean percentage	Same
			FDA approval package	Unclear			1.The mean IOP at baseline, week 2, month 1, month 2, month 3 of hour 0 and hour 2. 2. The percent mean IOP reduction from baseline at each time point. 3. AE.	NR	at week 2, month 1, month 2, month 3 of hour 0 and hour 2	IOP change from baseline	Mean percentage	Same

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Source	Primary outcomes	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
							4.visual acuity, visual field results, optic nerve cup-to-disc ratio, etc.					
3	21275 192024-008	74	Journal article	mean IOP at 8 am, 10 am, and 4 pm at week 2, week 6, and month 3	1. AE. 2. Biomicroscopy, iris pigmentation, visual acuity, blood pressure, and heart rate. 3.Ophthalmoscopic examinations as well as visual field, hematology, and blood chemistry evaluations.	1. Mean IOP reductions at 8 am, 10 am, and 4 pm at week 2, week 6, and month 3. 2. Response rates for all target IOPs at month 3. 3. AE. 4.Biomicroscopy, iris pigmentation, visual acuity, blood pressure, and heart rate. 5. Ophthalmoscopic examinations as well as visual field, hematology, and blood chemistry evaluations.		Goldmann applanation	at 8 am, 10 am, and 4 pm at week 2, week 6, and month 3	IOP	Mean	Same
			FDA approval package	mean IOP at 8 am, 10 am, and 4 pm at week 2, week 6, and month 3			1. Mean IOP reductions at 8 am, 10 am, and 4 pm at week 2, week 6, and month 3. 2. Response rates for all target IOPs at month 3. 3. AE. 4. Biomicroscopy, iris pigmentation, visual acuity, blood pressure, and heart rate. 5. Ophthalmoscopic examinations as well as visual field,	Goldmann applanation	at 8 am, 10 am, and 4 pm at week 2, week 6, and month 3	IOP	Mean	Same

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Source	Primary outcomes	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
							hematology, and blood chemistry evaluations.					
4	21275 192024-009	51	Journal article	IOP reduction from baseline at week 2, week 6, and month 3	1. AE. 2. Biomicroscopy, ophthalmoscopy, visual acuity, and visual field. 3. Heart rate and blood pressure, urinalysis and hematology/serum chemistry analysis. 4. At select centers, the following additional measures of ocular safety were performed: endothelial cell density and laser flare meter readings	1. Mean IOP at each follow-up visit. 2. Percentage of patients had sufficient IOP lowering to achieve desirable target IOP levels (<17 mmHg). 3. AE. 4. Biomicroscopy, ophthalmoscopy, visual acuity, and visual fields. 5. heart rate and blood pressure, urinalysis and hematology/serum chemistry analysis. 6. At select centers, the following additional measures of ocular safety were performed: endothelial cell density and laser flare meter readings		Goldmann applanation tonometry	at week 2, week 6, and month 3	IOP change(absolute and percentage) from baseline	Mean and mean percentage	Journal article: insufficient data for primary outcome reported. Different in values from Journal article and FDA (both using ITT): Between-group Differences in Mean IOP at 8 AM for Each Study Visit
			FDA approval package	IOP reduction from baseline at week 2, week 6, and month 3			1. Mean IOP at each time point. 2. AE. 3.Biomicroscopy, ophthalmoscopy, visual acuity, and visual fields. 4. Heart rate and blood pressure, urinalysis and hematology/serum chemistry analysis. 5. At select	Applanation tonometer	at week 2, week 6, and month 3	IOP change(absolute) from baseline	Mean	

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Source	Primary outcomes	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
							centers, the following additional measures of ocular safety were performed: endot+F6:H10helial cell density and laser flare meter readings					
5	20816 c-95-46	50	Journal article	Diurnally corrected IOP reduction from baseline, including peak and trough times at month 1, 2, and 3	1. Percentage of patients whose condition responded (IOP reduction>=5 mm Hg) or was controlled ((IOP<=21 mm Hg) on treatment at each time point. 2. Mean IOP at each time point. 3. AE and SAE. 4. Visual acuity, biomicroscopic parameters, funduscopic parameters, and visual fields. 5) Pulse and blood pressure, blood chemistry, hematology, and urinalysis.			Goldmann applanation tonometry	on 8am, 10am, 6pm at month 1, 2, and 3	IOP change from baseline	Mean	Journal article: mean IOP change in per protocol population.
			FDA approval package	Diurnally corrected IOP reduction from baseline, including peak and trough times at month 1, 2, and 3			1. Mean IOP at each time point. 2. Mean IOP at each time point categorized by age and gender. 3. AE. 4. Visual acuity, biomicroscopic parameters, funduscopic parameters, and visual fields. 5. Pulse and blood pressure, blood chemistry, hematology, and urinalysis.	NR	on 8am, 10am, 6pm at month 1, 2, and 3	IOP change from baseline	Mean	FDA: mean IOP change in so called ITT population (receiving treatment at least once)
6	20816 c-95-48	44	Journal article	Diurnally corrected IOP reduction from baseline, including peak and trough times at month 1, 2, and 3	1. Percentage of patients whose condition responded (IOP reduction>=5 mm Hg) or was controlled ((IOP<=21 mm Hg) on treatment at each time point. 2. Mean IOP at each time point. 3. AE. 4. Visual acuity, ocular signs, dilated fundus parameters, visual fields 5. Pulse, blood pressure, hematology, blood chemistry, urinalysis.			Goldmann applanation tonometry	on 8am, 10am, 6pm at month 1, 2, and 3	IOP change from baseline	Mean	Journal article: mean IOP change in per protocol population.

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Source	Primary outcomes	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
			FDA approval package	Diurnally corrected IOP reduction from baseline, including peak and trough times at month 1, 2, and 3			1. Mean IOP at each time point. 2. AE. 3. Visual acuity, ocular signs, dilated fundus parameters, visual fields. 4. Pulse, bloodpressure, hematology, blood chemistry, urinalysis.	NR	on 8am, 10am, 6pm at month 1, 2, and 3	IOP change from baseline	Mean	FDA: Mean IOP change in so called ITT population (receiving treatment at least once)
7	21214 C97-UIOS-005	64	Journal article	Mean change from baseline in 12-hour diurnal intraocular pressure at 6 months, defined as the arithmetic mean of intraocular pressures measured at pre dose and 2 (midmorning), 8 (afternoon), and 12 (evening) hours post instillation.	1. Mean changes from baseline in the four individual intraocular pressures. 2. percentage of patients who responded to therapy (that is,defined as having a reduction from baseline in 12-hour diurnal intraocular pressure >= 15%). 3. Best-corrected visual acuity, slit-lamp biomicroscopy, dilated ophthalmoscopy, manifest refraction, visual fields, evaluation of iris/eyelid discoloration and abnormal eyelash growth, ocular symptoms, ocular and nonocular adverse events, heart rate, and blood pressure.			Goldmann applanation tonometry	at month 6	IOP change from baseline	Mean diurnal IOP	available data in mean IOP by Study Visit (baseline and change from baseline) are the same.
			FDA approval package	Mea n IOP at each time point (8am, 10am, 4pm, 8pm) at week 2, 6, month3, 6 per FDA requirement			1. Mean changes from baseline in the four individual intraocular pressures. 2. Best-corrected visual acuity, slit-lamp biomicroscopy, dilated ophthalmoscopy, manifest refraction, visual fields, evaluation of iris/eyelid discoloration and abnormal eyelash growth,	NR	at each time point (8am, 10am, 4pm, 8pm) at week 2, 6, month3, 6 per FDA requirement	IOP	Mean	

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Source	Primary outcomes	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
							ocular symptoms, ocular and nonocular adverse events, heart rate, and blood pressure.					
8	21257 c-97-71	56	Journal article	mean IOP at 8 AM, 10 AM and 4 PM of week 2, month 1.5, 3, 4.5, 6, 9, 12 for the patient's worse eye	1. Mean changes from baseline at each time points. 2. The percentage of patients who responded to treatment (based on a 30% or greater intraocular pressure reduction from diurnal baseline or a final intraocular pressure of 17 mm Hg or less. 3。 SAE and AE. 4. Visual acuity, inflammatory cells and aqueous flare, ocular signs, fundus parameters, cup-to-disk ratio, or visual field parameters, corneal thickness or endothelial cell count, cystoid macular edema. 5. Pulse rate, blood pressure hematology, blood chemistry, and urinalysis.			Goldmann applanation tonometry	at 8 AM, 10 AM and 4 PM of week 2, month 1.5, 3, 4.5, 6, 9, 12	IOP	Mean	Same
			FDA approval package	mean IOP and mean IOP change from baseline at 8 AM, 10 AM and 4 PM of week 2, month 1.5, 3, 4.5, 6, 9, 12 for the patient's worse eye			1. Mean changes from baseline at each time points. 2. SAE and AE. 3. Visual acuity, inflammatory cells and aqueous flare, ocular signs, fundus parameters, cup-to-disk ratio, or visual field parameters, corneal thickness or endothelial cell count, cystoid macular edema. 4. Pulse rate, blood pressure hematology, blood chemistry, and urinalysis.	Applanation tonometry	at 8 AM, 10 AM and 4 PM of week 2, month 1.5, 3, 4.5, 6, 9, 12	IOP and IOP change from baseline	Mean	Same
9	21257 c-97-72	60	Journal article	mean IOP at 8 AM, 10 AM, and 4 PM of week 2	1. The mean IOP at 8 AM,10 AM,and 4 PM, pooled across visit days. 2. Mean changes from baseline at each			Goldmann applanatio	at 8 AM, 10 AM and 4 PM of	IOP	Mean	Mean IOP the same; mean IOP

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Source	Primary outcomes	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
				month 1.5, 3, 4.5, 6. month for the patient's worse eye	time points. 3. The mean changes from baseline at 8AM, 10AM, and 4PM, pooled across visit days. 4.The percentage of patients who responded to treatment (based on a 25% or greater intraocular pressure reduction from diurnal baseline. 5. SAE and AE. 6. Visual acuity, inflammatory cells and aqueous flare, ocular signs, fundus parameters, cup-to-disk ratio, or visual field parameters, corneal thickness or endothelial cell count, cystoid macular edema. 7. Pulse rate, blood pressure hematology, blood chemistry, and urinalysis.			n tonometry	week 2, month 1.5, 3, 4.5, 6			change from baseline slightly different
			FDA approval package	mean IOP and mean IOP change from baseline at 8 AM, 10 AM, and 4 PM of week 2 month 1.5, 3, 4.5, 6. month for the patient's worse eye			1. Mean changes from baseline at each time points. 2. AE and SAE. 3. Visual acuity, inflammatory cells and aqueous flare, ocular signs, fundus parameters, cup-to-disk ratio, or visual field parameters, corneal thickness or endothelial cell count, cystoid macular edema. 4) pulse rate, blood pressure hematology, blood chemistry, and urinalysis.	Applanation tonometry	at 8 AM, 10 AM and 4 PM of week 2, month 1.5, 3, 4.5, 6	IOP and IOP change from baseline	Mean	
10	21257 c-97-79	54	Journal article	mean IOP at 9 AM, 11 AM, 4AM of week 2 month 1.5, 3, 4.5, 6, 9.	1. AE. 2. Visual acuity, ocular hyperemia, aqueous flara and inflammatory cells, ocular signs, dilated fundus examination, visual fields,	1. Mean IOP change from baseline at individual visits. 2. Percentage of patients responded to treatmen (IOP decreased by at		Goldmann applanation tonometry	at 9 AM, 11 AM, 4AM of week 2 month 1.5, 3, 4.5, 6, 9.	IOP	Mean	Same

No.	Drugs@FDA NDA-Protocol number	Reference ID¶	Source	Primary outcomes	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from FDA)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
					pigmentation and eyelash characteristics. 3. Pulse rate and blood pressure	least 6 mm Hg or measured IOP was 20 mm Hg or lower). 3. AE. 4. Visual acuity, ocular hyperemia, aqueous flara and inflammatory cells, ocular signs, dilated fundus examination, visual fields, pigmentation and eyelash characteristics. 5. Pulse rate and blood pressure						

Legend:
1. ¶ See Appendix 2 for reference ID
2. ROB: risk of bias
3. IOP: intraocular pressure
4. Color coding:

M	Misleading
X	Substantive difference across reports
J	Difference in completeness across reports, the journal article provides more information
F	Difference in completeness across reports, the FDA approval package provides more information
E	Difference in completeness across reports, each provides some information
	No difference across reports

Table 7. Comparison of reporting of trials (bibliographic databases vs ClinicalTrials.gov) Part 1

No.	ClinicalTrials.gov identifier	Reference ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	RoB assessment for allocation concealment	Masking of IOP assessor	Funding for the study	Number of study groups	Treatments compared	Sample size at baseline	Age	Sex	Availability of outcome data			
																			IOP	Visual field	Vertical cup/ discratio	Central visual acuity
1	NCT00277498	61	J			J	J	J	J			J			J	J	J	J	J			
2	NCT00751049	35				J			J						J	J	J	J	J			
3	NCT00751062	27							J					X	X	J	J	J	J			
4	NCT00751127	69	C			J	J						J		J	J			J			
5	NCT01026831	108	E	J		J	J	C	J	J	J	J					C					
6	NCT01155219	110	J				J	C					C				C	C	J			
7	NCT01253902	109	C			J	J	C									C		J			
8	NCT00539526	104	E				J	C									J	J	J			
9	NCT01223378	113	J	J	M	J	J							J	J	J	J	J	J			
10	NCT01254604	114	E	J					J	J	J						J					
11	NCT00690794	101	J			J			J	J	J				M		E					
12	NCT00991822	98	M		X										X				J			

Table 7. Comparison of reporting of trials (bibliographic databases vs ClinicalTrials.gov) Part 1 details

No.	ClinicalTrials.gov identifier	Reference ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
1	NCT00277498	61	B1b-B1m. 1) Inclusion criteria. Journal article: pigmentary and pseudoexfoliative glaucoma; the mean IOP was required to be 26 through 36 mmHg in the eye with the higher IOP. ClincalTrials.gov: NR. 2) Exclusion cirteria. Journal article: any ocular filtering surgical intervention; "ocular procedure within 3 months before screening". ClincalTrials.gov: NR. 3) Other eligibility criteria. Journal article: yes. ClincalTrials.gov: no			Power calculation. Journal article: Reported. ClincalTrials.gov: NR	Journal article: intention-to-treat, "At least receiving one treatment/intervention", "Eligible population", "Safety population" or "Safety analysis". ClincalTrials.gov: NR	Journal article: reported. ClincalTrials.gov:NR	Journal article: reported. ClincalTrials.gov: NR		IOP assessor masking. Journal article: yes. ClincalTrials.gov: NR.	
2	NCT00751049	35				Power calculation. Journal article: Reported. ClincalTrials.gov: NR			Journal article: reported. ClincalTrials.gov: NR			
3	NCT00751062	27							Journal article: reported. ClincalTrials.gov: NR			
4	NCT00751127	69	B1b-B1m 1)Inclusion criteria. ClincalTrials.gov: capsular glaucoma, pigmentary glaucoma; IOP>=22; age>=40. Journal article: NR. 2) Exclusion criteria: ClincalTrials.gov: history of acute angle closure; regular B-adrenergic antagonist treatment for >3m and/or at any time during 6m prior to study start. Journal article: NR.				Journal article: "Intention-to-treat", "Responders". ClincalTrials.gov: NR					Journal article: Department, institution, or organization. ClincalTrials.gov: NR
5	NCT01026831	108	B1b-B1m 1) Inclusion criteria. IOP. Journal	Journal article: reported.		Power calculation.	Journal article: per	Journal article: NR.	Journal article: reported.	Journal article: reported.	IOP assessor	

No.	ClinicalTrials.gov identifier	Reference ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
			article: Specified that the IOP requirement was after the discontinuation of any existing ocular hypotensive treatment. ClincalTrials.gov: did not specify. Prior glaucoma medication. Both include patient who is drug-naive. But ClincalTrials.gov gave a definition for drug-naive (those who have never used or who have not used ocular hypotensive medication for at least 4 weeks prior to screening). 2) Exclusion critetia. Prior glaucoma medication. Journal article: ocular medications (other than antiglaucoma medications or topical lubricants) within 1 week of screening. ClincalTrials.gov: Patient is currently taking two or more anti-glaucoma medications (except Cosopt™ or its generic formulation); Patient has previously used tafluprost. Prior ocular surgery. Journal article: history of certain ocular surgeries. ClincalTrials.gov: Patient has had intraocular surgery in either eye in the last 4 months; Patient has a history of glaucoma surgery or refractive surgery in either eye	ClincalTrials.gov: NR		Journal article: Reported. ClincalTrials.gov: NR	protocol and "At least receiving one treatment/intervention". ClincalTrials.gov: per protocol	ClincalTrials.gov: reported	ClincalTrials.gov: NR	ClincalTrials.gov: NR	masking. Journal article: yes. ClincalTrials.gov: NR.	
6	NCT01155219	110	B1b-B1m 1) Inclusion criteria. IOP. Journal article: the study population included patients...with an intraocular pressure <= 18 mmHg in both eyes. ClincalTrials.gov: NR. 2) Exclusion criteria.				Journal article: per protocol, full analysis set. ClincalTrials.gov: full analysis set	Journal article: NR. ClincalTrials.gov: reported				Journal article: NR. ClincalTrials.gov: reported

No.	ClinicalTrials.gov identifier	Reference ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
			Prior glaucoma medication. Journal article: Systemic antiglaucoma treatment was not allowed within the last month and during the treatment period. ClincalTrials.gov: NR									
7	NCT01253902	109	B1b-B1m. Exclusion criteria: Journal article: history of refractive surgery. ClincalTrials.gov: Intraocular surgery or glaucoma laser surgery in study eye(s) within 3 months. History of corneal refractive laser surgery (eg. LASIK, LASEK) in study eye(s).			Power calculation. Journal article: Reported. ClincalTrials.gov: NR	Journal article: intention-to-treat, "Per protocol", "Safety population" or "Safety analysis". ClincalTrials.gov: "Intention-to-treat"	Journal article: NR. ClincalTrials.gov: reported				
8	NCT00539526	104	B2. Did eligibility criteria REQUIRE taking an ocular hypotensive medication at the time of enrollment? Journal article: yes. ClincalTrials.gov: no. B3. Did eligibility criteria ALLOW enrolling participants if they were on ocular hypotensive medication at the time of enrollment? Journal article:yes. ClincalTrials.gov: can't tell. B1b-B1m. 1) Inclusion criteria: Secondary glaucoma (pigmentary, pseudoexfoliative glaucoma). Journal article: NR. ClincalTrials.gov: yes. Prior glaucoma medication. Journal article:Patients at least 18 years old with a diagnosis of openangle glaucoma or OHT who had been on				Journal article: "Per protocol". ClincalTrials.gov: NR.	Journal article: NR. ClincalTrials.gov: reported				

No.	ClinicalTrials.gov identifier	Reference ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
			bilateral latanoprost for at least 4 weeks were eligible for the study. Patients on latanoprost and 1 adjunctive medication at screening were also eligible, but were required to undergo a 4-week washout of the adjunctive medication before the baseline visit. ClincalTrials.gov: no. 2) Exclusion criteria: Prior glaucoma medication. Journal article: use of bimatoprost or travoprost within the previous 6 months, required use of ocular medications other than the study medications during the study (intermittent use of BAK-free artificial tears was permitted). ClincalTrials.gov:no. Prior cataract surgery. Journal article: history of refractive surgery. ClincalTrials.gov: no.									
9	NCT01223378	113	B1b-B1m. 1) Inclusion criteria. IOP. Journal article: "Subjects were eligible if they had an IOP of 22–32 mm Hg, and an IOP of ≥24 mm Hg for at least two of three measurements during Visit 3 (Day 1, baseline), which occurred after a 28-day washout period in subjects previously treated with IOP-lowering medications." ClincalTrials.gov: NR 2) Exclusion Criteria. Angle closure glaucoma. Journal article: subjects with closed or barely open anterior chamber angle or a history of acute angle closure in either eye.	Countries in which participants were recruited. Journal article: US; Bulgaria; Poland; Czech Republic. ClincalTrials.gov: US	Journal article: 29 days. ClincalTrials.gov: 28 days.	Journal article: reported.ClincalTrials.gov: NR	Journal article: "Intention-to-treat". "Safety population" or "Safety analysis". ClincalTrials.gov: NR.					

No.	ClinicalTrials.gov identifier	Reference ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
			ClincalTrials.gov: NR B3.Did eligibility criteria ALLOW enrolling participants if they were on ocular hypotensive medication at the time of enrollment? Journal article:yes. ClincalTrials.gov:no									
10	NCT01254604	114	1) Inclusion criteria. ClincalTrials.gov: Mean IOP >36 mmHg in either eye at screening. Journal article: NR. 2) Exclusion criteria. Journal article: Subjects on glaucoma treatment at the time of screening visit (visit 1) underwent a washout of previous glaucoma treatment; following this, at the baseline visit (visit 2), the subjects' mean (or median) IOP had to be ≥ 24 and ≤ 36 mmHg in at least one eye at the 08:00 hour time point, and there had to be a < 5 mmHg difference in mean (or median) IOP between the eyes at the 08:00, 10:00 and 16:00 hour time points. ClincalTrials.gov: NR	Journal article: reported.Clincal Trials.gov: NR					Journal article: reported.Clincal Trials.gov: NR	Journal article: reported.Clincal Trials.gov: NR		
11	NCT00690794	101	B1b-B1m. Exclusion criteria. Prior glaucoma medication. Journal article: if they had used any ocular medications (other than latanoprost 0.005% or artificial tears) within seven days of the screening visit. ClincalTrials.gov: NR. Prior ocular surgery. Journal article: prior corneal surgery within the previous one year; any intraocular surgery within the previous six months;			Journal article reported.Clincal Trials.gov: NR			Journal article: reported.Clincal Trials.gov: NR	Journal article: reported.Clincal Trials.gov: NR		

No.	ClinicalTrials.gov identifier	Reference ID¶	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
			any ocular laser surgery within the previous three months. ClincalTrials.gov: NR									
12	NCT00991822	98	1) Inclusion criteria. IOP. Journal article: >22 mmHg in at least one eye. ClincalTrials.gov: >21 mmHg in at least one eye. Age. ClincalTrials.gov >19. Journal article: NR.		Journal article: 6 months. ClincalTrials.gov: 3 months							

Table 7. Comparison of reporting of trials (bibliographic databases vs ClinicalTrials.gov) Part 1 details (continued)

No.	ClinicalTrials.gov identifier	Reference ID¶	Number of study groups	Treatments compared	Sample size at baseline	Age	Sex	Availability of outcome data			
								IOP	Visual field	Vertical cup/disc ratio	Central visual acuity
1	NCT00277498	61		Number of participants randomized. Journal article: reported. ClincalTrials.gov: NR. Placebo usage (account for different administration time of latanoprost/combination and timolol). Journal article: reported. ClincalTrials.gov: NR	Journal article: reported. ClincalTrials.gov: NR.	Journal article: reported. ClincalTrials.gov: NR.	Journal article: reported. ClincalTrials.gov: NR.	Journal article: yes, ClincalTrials.gov: no.			
2	NCT00751049	35		Number of participants randomized. Journal article: reported. ClincalTrials.gov: NR. Placebo usage (account for different administration time of latanoprost/combination and timolol). Journal article: reported. ClincalTrials.gov: NR. Drug dose. Journal article: reported. ClincalTrials.gov: NR	Journal article: reported. ClincalTrials.gov: NR.	Journal article: reported. ClincalTrials.gov: NR.	Journal article: reported. ClincalTrials.gov: NR.	Journal article: yes, ClincalTrials.gov: no.			
3	NCT00751062	27	Publication: 3. ClincalTrials.gov 2.	Arms. Journal article: 3 arms, timolol, latanoprost morning 3m then evening 3m, latanoprost evening 3m then morning 3m. ClincalTrials.gov: 2 arms, latanoprost, timolol. Number of participants randomized. Journal article: reported. ClincalTrials.gov: NR. Placebo usage (account for different administration time of lanaprost and timolol). Journal article: reported. ClincalTrials.gov: NR. Drug dose. Journal article: reported. ClincalTrials.gov: NR. Frequency. Journal	Journal article: reported. ClincalTrials.gov: NR.	Journal article: reported. ClincalTrials.gov: NR.	Journal article: reported. ClincalTrials.gov: NR.	Journal article: yes, ClincalTrials.gov: no.			

No.	ClinicalTrials.gov identifier	Reference ID¶	Number of study groups	Treatments compared	Sample size at baseline	Age	Sex	Availability of outcome data			
								IOP	Visual field	Vertical cup/disc ratio	Central visual acuity
				article: reported. ClincalTrials.gov: NR.							
4	NCT00751127	69		Drug dose. Journal article: reported. ClincalTrials.gov: NR.	Journal article: reported. ClincalTrials.gov : NR.			Journal article: yes, ClincalTrials.gov : no.			
5	NCT01026831	108				Journal article: age each arm. CT: age in each arm and in total					
6	NCT01155219	110				Journal article: age in total. CT: age in each arm and in total	Journal article: sex in total. CT: sex in each arm and in total	Journal article: yes, ClincalTrials.gov : no.			
7	NCT01253902	109				Journal article: age in each arm. CT: age in each arm and in total		Journal article: yes, ClincalTrials.gov : no.			
8	NCT00539526	104		%		Journal article:mean and sd. ClincalTrials.gov : mean		Journal article: reported. ClincalTrials.gov : NR			
9	NCT01223378	113	Journal article: 5 groups. 4 groups of one drug; 1 group of the other drug. ClincalTrials.gov : 2 groups.	Journal article: Latanoprostene 0.006%; 0.012%; 0.024%;0.040%. Latanoprost 0.005%. ClincalTrials.gov: BOL-303259-X; Latanoprost 0.005%.	Journal article: reported. ClincalTrials.gov : NR.	Journal article: reported. ClincalTrials.gov : NR.	Journal article: reported. ClincalTrials.gov : NR.	Journal article: reported. ClincalTrials.gov : NR			
10	NCT01254604	114				Journal article: mean and SD of age in each arm. ClincalTrials.gov : mean and SD of age in each arm and in total.					
11	NCT00690794	101		Number of participants randomized. Journal article: 724. ClincalTrials.gov: 726 (363:363).		Journal article: categorical. ClincalTrials.gov : continous					
12	NCT00991822	98		Number of participants randomized. Journal article: 140 (70:70). ClincalTrials.gov:160. Drug dose. ClincalTrials.gov: reported. Journal article: NR.				Journal article: reported. ClincalTrials.gov : NR			

Table 7. Comparison of reporting of trials (bibliographic databases vs ClinicalTrials.gov) Part 2

No.	ClinicalTrials.gov identifier	Reference ID ¶	Source	Primary outcome	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from CT.gov)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
1	NCT01026831	108	Journal article	The mean IOP change from baseline at all 9 time points during the study (08:00, 10:00, and 16:00 hours at weeks 2, 6, and 12)	1. The proportion of patients with a favorable IOP response, defined as >=25% reduction in diurnal IOP from baseline at weeks 2, 6, and 12. Diurnal IOP was calculated as the mean of the IOPs in the "study eye" at the 3 time points for each clinic visit (08:00, 10:00, 16:00 hours). 2. The mean change from baseline in diurnal IOP at weeks 2, 6, and 12. 3. Safety and tolerability were primarily assessed by counts and clinical review of adverse events within 14 days after the last dose of treatment (or after discontinuation). The proportion of patients who reported 1 or more adverse events, a drug-related adverse event, or a serious adverse event; patients who discontinued because of an adverse event; and adverse events reported by at least 4 patients in any treatment group were calculated. The following groupings of adverse events were prespecified as being of special interest: conjunctival hyperemia, ocular pain/stinging/irritation, and ocular pruritus.			Goldmann applanation tonometer.	08:00, 10:00, and 16:00 hours at week 2, 6, and 12 clinic visits	IOP change from baseline	Mean	Same
			ClinicalTrials.gov	Mean Intraocular Pressure (IOP) Change From Baseline at All 9 Time Points During the Study (0800, 1000 and 1600 Hrs at Weeks 2, 6, and 12)			Baseline IOP; SAE and other AE	Goldmann applanation tonometer.	0800, 1000 and 1600 Hrs at Weeks 2, 6, and 12	IOP change from baseline	Mean	Same
2	NCT01155219	110	Journal article	A combination of satisfactory or acceptable effect on IOP and a reduction of at least 20% of the total tolerance score on Day 84 in the worse eye	Sum of scores of signs and symptoms, assessment of global discomfort and tolerance by the patient, assessment of both efficacy and tolerance by the patient, assessment of both the efficacy and tolerance by the investigator, AE, number of withdrawals, and comparison of the mean basal IOP after 28 days of treatment.	**1. Baseline IOP, visual acuity.** 2. a combination of satisfactory or acceptable effect on IOP and a reduction of at least 20% of the total tolerance score on Day 28 in the worse eye. 3. Comparison of the mean basal IOP at Day 28 day and day 84 of treatment. 4. Satisfactory or acceptable effect on IOP score. 5. sum of scores of signs and symptoms. 6. assessment of tolerance by the patient. 7. assessment of global efficacy by the investigator		Unclear	D28, D84	IOP	Mean	Reported
			ClinicalTrials.gov	Ocular Tolerance [Time Frame: Day 84]: Response			SAE and other AE	NR	NR	NR	NR	NR

No.	ClinicalTrials.gov identifier	Reference ID ¶	Source	Primary outcome	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from CT.gov)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
				defined as a combination of satisfactory or acceptable effect on IOP and a reduction of at least 20% of the total tolerance score in the worse eye.								
3	NCT01253902	109	Journal article	Bulbar conjunctival hyperemia at week 12	corneal staining with fluorescein and TBUT. IOP measurements and adverse events.	**1. change from baseline in conjunctival hyperemia at 1 week.** 2. Mean corneal staining score at baseline, 12 weeks. 3. Change from baseline in mean corneal staining score. 4. Mean TBUT at baseline, 12 weeks. 5. Change from baseline in mean TBUT. **6. Percentage of patients with no change or a decrease in conjunctival hyperemia from baseline. 7. Percentage of patient with a ≥1-unit increase in conjunctival hyperemia from baseline at week 12. 8. Change from baseline at week 1, 4, and 12 in mean IOP. 9. AE**		NR	Week 1,4,12	IOP change from baseline	Mean	Reported
			ClinicalTrials.gov	Mean Conjunctival Hyperemia at Week 12			Mean Corneal Staining With Fluorescein at Week 12; Mean Tear Break Up Time (TBUT) at Week 12; SAE and other AE	NR	NR	NR	NR	NR
4	NCT00539526	104	Journal article	conjunctival hyperemia at month 3.	corneal staining with fluorescein, tear breakup time(TBUT), and IOP.	**1. mean conjunctival hyperemia scores at baseline and at any follow-up visit. 2. change from baseline conjunctival hyperemia scores at week 1, month 1, and month 3.** 3. mean corneal staining at baseline and at any follow-up visit. 4. change from baseline mean corneal staining at week 1, month 1, and month 3. 5. mean TBUT at baseline and at any follow-up visit. 6.change from baseline mean TBUT at week 1, month 1, and month 3. 7.mean IOP at baseline and at any follow-up visit. 8. change from baseline mean IOP at week 1, month 1, and month 3. **9. SAE and AE**		NR	Week 1, month 1, month 3	IOP change from baseline	Mean	reported

No.	ClinicalTrials.gov identifier	Reference ID ¶	Source	Primary outcome	Other outcomes (from method section of Publication)	Other outcomes (from results section of Publication)	Other outcomes (from CT.gov)	IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
			ClinicalTrials.gov	Change From Baseline in Mean Conjunctival Hyperemia Scores at Month 3			1. Change From Baseline in Corneal Staining With Fluorescein at Month 3. 2. Change From Baseline in Tear Break-Up Time (TBUT) at Month 3. 3. SAE and AE	NR	NR	NR	NR	NR
5	NCT01254604	114	Journal article	mean diurnal IOP change from baseline at week 4 in the study eye.	1. proportion of subjects with ≥ 25%reduction in IOP from baseline to week 4. 2. AE	1. proportion of subjects with ≥ 25%reduction in IOP from baseline to week 4. 2. Incidences of Adverse Event (AE) [Time Frame: Up to 14 days after Week 4 visit]. 3. Incidences of Study Drug Discontinuation Due to an AE [Time Frame: Up to Week 4] 4. SAE and other AE		Goldmann applanation tonometer	IOP was measured at Week 4 at 0800, 1000 and 1600 hours.	Mean Diurnal IOP Change From Baseline	Mean Diurnal IOP	Same
			ClinicalTrials.gov	Mean Diurnal IOP Change From Baseline at Week 4 - Study Eye			1. Number of Participants With an Adverse Event (AE) [Time Frame: Up to 14 days after Week 4 visit]. 2. Number of Participants Who Discontinued Study Drug Due to an AE [Time Frame: Up to Week 4]. 3. Number of Participants With ≥25% Reduction in IOP From Baseline to Week 4 - Study Eye. 4. SAE and other AE	Goldmann applanation tonometer	IOP was measured at Week 4 at 0800, 1000 and 1600 hours.	Mean Diurnal IOP Change From Baseline	Mean Diurnal IOP	Same

Legend:
1. ¶ See Appendix 2 for reference ID
2. ROB: risk of bias
3. IOP: intraocular pressure
4. Color coding:

M	Misleading
X	Substantive difference across reports
J	Difference in completeness across reports, the journal article provides more information
C	Difference in completeness across reports, the ClinicalTrials.gov registration provides more information
E	Difference in completeness across reports, each provides some information
	No difference across reports

Table 8. Comparison of trial reporting (Drugs@FDA vs ClinicalTrials.gov) Part 1

No.	Drugs@FDA NDA-Protocol number	ClinicalTrials.gov identifier	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	RoB assessment for allocation concealment	Masking of IOP assessor	Funding for the study	Number of study groups	Treatments compared	Sample size at baseline	Age	Sex	Availability of outcome data			
																			IOP	Visual field	Vertical cup/disc ratio	Central visual acuity
1	204251c-09-038	NCT00961649	C	C				C				C						C				

Table 8. Comparison of reporting of trials (Drugs@FDA vs ClinicalTrials.gov) Part 1 details

No.	Drugs@FDA NDA-Protocol number	ClinicalTrials.gov identifier	Eligibility criteria	Region or country of recruitment	Maximum length of follow-up after randomization	Sample size calculation	Types of analysis described	Participants flow diagram	Description of sequence generation	Description of allocation concealment	Masking of IOP assessor	Funding for the study
1	204251 c-09-038	NCT00961649	Inclusion Criteria. ClinicalTrials.gov: diagnosis of open-angle glaucoma or ocular hypertension, with mean intraocular pressure within protocol-specified range at eligibility visit/s. FDA: NR. Exclusion Criteria. ClinicalTrials.gov: any form of glaucoma other than open-angle glaucoma; ocular surgery within the preceding 6 months; ocular laser surgery within the preceding 3 months. FDA:NR	ClinicalTrials.gov: reported. FDA: NR				ClinicalTrials.gov: yes. FDA: no			ClinicalTrials.gov: participant, care provider, investigator, outcome assessor were masked. FDA: participant, observer were masked.	

Table 8. Comparison of reporting of trials (Drugs@FDA vs ClinicalTrials.gov) Part 1 details (continued)

No.	Drugs@FDA NDA-Protocol number	ClinicalTrials.gov identifier	Number of study groups	Treatments compared	Sample size at baseline	Age	Sex	Availability of outcome data			
								IOP	Visual field	Vertical cup/disc ratio	Central visual acuity
1	204251 c-09-038	NCT00961649		Placebo usage. ClinicalTrials.gov: reported. FDA: NR			ClinicalTrials.gov: reported. FDA: NR				

Table 8. Comparison of reporting of trials (Drugs@FDA vs ClinicalTrials.gov) Part 2

No.	Drugs@FDA NDA-Protocol number	ClinicalTrials.gov identifier	Source	Primary outcomes	Other outcomes (from FDA)		Other outcomes (from CT.gov)		IOP measurement (just the scale)	IOP time point (when the comparison was made)	IOP metric	IOP aggregation	Quantitative results for the primary outcome(s)
1	204251 c-09-038	NCT00961649	FDA approval package	mean IOP at each assessment time points (8 AM, + 2 hrs, + 7 hrs, and + 9 hrs) at Week 6	AE and SAE; dropouts and/or Discontinuations; cardiovascular parameters (systolic blood pressure, diastolic blood pressure and heart rate)				NR		IOP	Mean	mean IOP at week 6
			ClinicalTrials .gov	Mean Change in Intraocular Pressure (IOP) From Baseline to Each of the Assessment Time Points (8 AM, + 2 Hrs, + 7 Hrs, and + 9 Hrs) at Week 6			SAE and other AE		Goldmann applanation tonometry		IOP change from baseline	Mean	Mean IOP change from baseline at week 6

Legend:
1. ROB: risk of bias
2. IOP: intraocular pressure
3. Color coding:

M	Misleading
X	Substantive difference across reports
F	Difference in completeness across reports, the FDA approval package provides more information
C	Difference in completeness across reports, the ClinicalTrials.gov registration provides more information
E	Difference in completeness across reports, each provides some information
	No difference across reports

Table 9. Strengths and limitations of data sources

Source	Strengths	Limitations
PICO information (patient, intervention, comparison, outcome)		
Bibliographic databases	• Include a large number of trials and participants • Provide detailed descriptions for interventions (e.g., dose, schedule)	• Provide limited information about secondary outcomes and adverse events of trials
Drugs @FDA	• Provide information about secondary outcomes and adverse events that may not be available elsewhere • Useful for identifying unpublished trials for regulated products	• Only useful for products regulated by FDA • Approval packages prior to 1997 not readily available online • Description of interventions may be incomplete
ClinicalTrials.gov	• Useful for identifying unpublished trials on all types of interventions (including interventions not regulated by FDA) • Provide PICO in a tabulated format	• Not all trials (and interventions evaluated in those trials) prior to 2000 are available • Registration may be incomplete; not all results are available • Provide limited information about secondary outcomes and adverse events of trials
Design, statistical methods, and risk of bias information		
Bibliographic databases	• Provide most information about the trial design, statistical methods, and for assessing risk of bias	
Drugs @FDA		• Provide limited information about the trial design; usually contain more information about missing data (and how they were handled; sometimes useful for assessing risk of bias
ClinicalTrials.gov		• Provide least information about the trial design, statistical methods; not useful for assessing risk of bias

Reporting of results		
Bibliographic databases	• Almost always provide information about baseline characteristics • Provide reasonably complete information about result and precision measures	• Patient flow diagram not always available
Drugs @FDA	• Provided results at all time points	• Provided limited information about baseline characteristics or patient flow • Precision measures may not be reported
ClinicalTrials.gov	• Provide detailed information about patient flow	• Provide limited information about baseline characteristics • Results may not be posted
Time and resources needed for trial identification and data extraction		
Bibliographic databases		• Substantial amount of time and resources needed for trial identification and data extraction
• Drugs@FDA	• Efficient for trial identification	• Some obstacles for data extraction because of unstructured format for results reporting
• ClinicalTrials.gov	• Efficient for trial identification • Most efficient for data extraction when results are reported in a structured format	

Table 10.1. Summary estimates of mean difference in IOP at 3 months derived from pairwise meta-analysis (all unique trials)

Column1	Column2	No. of studies	Comparison-Specific Heterogeneity					Common heterogeneity*		
			Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared	Mean difference	95% CI, lower	95% CI, upper
vs. Placebo/Vehicle/No treatment	Brimonidine	1	-2.30	-3.99	-0.61	NA	NA	-2.30	-4.50	-0.10
	Betaxolol	3	-2.28	-3.65	-0.91	1.16	79%	-2.24	-3.26	-1.23
	Levobunolol	2	-7.51	-8.53	-6.50	0.00	0%	-7.44	-8.92	-5.96
	Timolol	5	-3.61	-4.63	-2.59	0.76	58%	-3.58	-4.50	-2.67
	Levobetaxolol	1	-3.00	-4.53	-1.47	NA	NA	-3.00	-5.08	-0.92
	Brinzolamide	1	-2.28	-4.04	-0.52	NA	NA	-2.28	-4.54	-0.02
	Dorzolamide	3	-1.33	-1.68	-0.98	0.00	0%	-1.57	-2.74	-0.39
	Bimatoprost	1	-4.60	-5.60	-3.60	NA	NA	-4.60	-6.31	-2.89
	Unoprostone	1	-0.50	-1.70	0.70	NA	NA	-0.50	-2.34	1.34
vs. Apraclonidine	Timolol	2	-1.76	-3.27	-0.26	0.45	28%	-1.76	-3.31	-0.21
vs. Brimonidine	Betaxolol	1	-0.04	-1.03	0.95	NA	NA	-0.04	-1.74	1.66
	Timolol	4	-0.75	-2.15	0.66	1.72	94%	-0.76	-1.58	0.06
	Brinzolamide	4	-0.36	-1.43	0.71	0.97	84%	-0.32	-1.14	0.50
	Latanoprost	5	-1.08	-2.12	-0.05	1.13	83%	-1.16	-1.92	-0.40
	Travoprost	1	-1.20	-3.77	1.37	NA	NA	-1.20	-4.16	1.76
vs. Betaxolol	Levobunolol	2	-4.73	-10.01	0.55	12.25	83%	-3.32	-5.17	-1.47
	Timolol	8	-1.70	-2.41	-0.99	0.38	39%	-1.71	-2.47	-0.95
	Levobetaxolol	1	-2.00	-3.54	-0.46	NA	NA	-2.00	-4.08	0.08
	Dorzolamide	2	-0.30	-0.96	0.36	0.00	0%	-0.35	-1.54	0.84

Column1	Column2	No. of studies	Comparison-Specific Heterogeneity					Common heterogeneity*		
			Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared	Mean difference	95% CI, lower	95% CI, upper
	Latanoprost	2	-1.05	-2.62	0.51	0.33	25%	-1.05	-2.73	0.63
vs.Carteolol	Levobunolol	1	-2.90	-4.59	-1.22	NA	NA	-2.90	-5.10	-0.70
	Timolol	4	0.03	-0.61	0.68	0.11	24%	0.06	-0.85	0.97
vs. Levobunolol	Timolol	11	-0.03	-0.44	0.39	0.01	3%	-0.01	-0.65	0.63
vs. Timolol	Levobetaxolol	3	1.25	0.27	2.23	0.52	73%	1.26	0.30	2.23
	Brinzolamide	2	0.78	-1.04	2.61	1.00	41%	0.95	-0.48	2.38
	Dorzolamide	6	1.20	0.52	1.88	0.39	56%	1.20	0.47	1.94
	Bimatoprost	7	-2.09	-2.48	-1.71	0.05	19%	-2.22	-2.87	-1.57
	Latanoprost	14	-1.26	-1.68	-0.85	0.34	64%	-1.28	-1.75	-0.81
	Travoprost	7	-0.93	-1.30	-0.57	0.00	0%	-0.93	-1.61	-0.24
	Tafluprost	2	-0.93	-2.29	0.44	0.83	85%	-0.88	-1.98	0.21
	Unoprostone	3	1.43	0.39	2.47	0.72	86%	1.44	0.56	2.33
vs. Brinzolamide	Dorzolamide	2	0.32	-0.17	0.80	0.00	0%	0.30	-0.78	1.39
	Travoprost	1	-2.70	-3.99	-1.41	NA	NA	-2.70	-4.60	-0.80
vs. Dorzolamide	Latanoprost	1	-2.90	-3.70	-2.10	NA	NA	-2.90	-4.49	-1.31
vs. Bimatoprost	Latanoprost	7	0.92	0.14	1.69	0.72	71%	0.90	0.21	1.59
	Travoprost	10	0.53	-0.08	1.15	0.61	68%	0.53	-0.04	1.11
vs. Latanoprost	Travoprost	8	-0.11	-0.49	0.27	0.00	0%	-0.10	-0.75	0.56
	Tafluprost	1	-0.90	-3.40	1.60	NA	NA	-0.90	-3.80	2.00
	Unoprostone	6	3.07	2.51	3.63	0.01	2%	2.95	2.12	3.78

Legend:
1. NA: Not applicable
2. There are 110 two-arm trials, 10 three-arm trials, and 1 four-arm trial
3. Mean difference is calucated using the IOP of the drug in column2-column1

4. Tau square: between-study variance in random-effect models; I square: proportion of variance due to heterogeneity
5. Glaucoma drugs are expected to lower IOP; therefore, mean difference >0 favors the drug in column 1, and mean difference <0 favors the drug in column 2.
6. *Estimated tau square is 0.4648; estimated I square is 64.17%
7.Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 10.2. Summary estimates of mean difference in IOP at 3 months derived from pairwise meta-analysis (Published trials)

Column1	Column2	No. of studies	Comparison-Specific Heterogeneity					Common heterogeneity*		
			Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared	Mean difference	95% CI, lower	95% CI, upper
vs. Placebo/Vehicle/No treatment	Brimonidine	1	-2.30	-3.99	-0.61	NA	NA	-2.30	-4.49	-0.11
	Betaxolol	2	-2.90	-4.65	-1.15	1.30	81%	-2.79	-4.00	-1.58
	Levobunolol	2	-7.51	-8.53	-6.50	0.00	0%	-7.44	-8.91	-5.97
	Timolol	4	-3.90	-5.12	-2.69	0.85	56%	-3.89	-4.95	-2.83
	Brinzolamide	2	-1.75	-2.76	-0.75	0.00	0%	-1.81	-3.24	-0.39
	Dorzolamide	4	-1.38	-1.72	-1.04	0.00	0%	-1.69	-2.68	-0.69
	Bimatoprost	1	-4.60	-5.60	-3.60	NA	NA	-4.60	-6.30	-2.90
	Unoprostone	1	-0.50	-1.70	0.70	NA	NA	-0.50	-2.33	1.33
vs. Apraclonidine	Timolol	2	-1.76	-3.27	-0.26	0.45	28%	-1.76	-3.30	-0.22
vs. Brimonidine	Betaxolol	1	-0.04	-1.03	0.95	NA	NA	-0.04	-1.73	1.65
	Timolol	4	-0.75	-2.15	0.66	1.72	94%	-0.76	-1.57	0.06
	Brinzolamide	2	0.00	-2.16	2.15	2.25	93%	-0.01	-1.14	1.12
	Latanoprost	5	-1.08	-2.12	-0.05	1.13	83%	-1.16	-1.91	-0.40
	Travoprost	1	-1.20	-3.77	1.37	NA	NA	-1.20	-4.14	1.74
vs. Betaxolol	Levobunolol	2	-4.73	-10.01	0.55	12.25	83%	-3.32	-5.16	-1.48
	Timolol	8	-1.54	-2.24	-0.83	0.43	50%	-1.54	-2.27	-0.82
	Dorzolamide	2	-0.30	-0.96	0.36	0.00	0%	-0.35	-1.53	0.84
	Latanoprost	2	-1.05	-2.62	0.51	0.33	25%	-1.05	-2.72	0.63
	Unoprostone	1	0.60	0.09	1.11	NA	NA	0.60	-0.86	2.06

Column1	Column2	No. of studies	Comparison-Specific Heterogeneity					Common heterogeneity*		
			Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared	Mean difference	95% CI, lower	95% CI, upper
vs. Carteolol	Levobunolol	1	-2.90	-4.59	-1.22	NA	NA	-2.90	-5.09	-0.71
	Timolol	4	0.03	-0.61	0.68	0.11	24%	0.06	-0.85	0.97
vs. Levobunolol	Timolol	11	-0.03	-0.44	0.39	0.01	3%	-0.01	-0.64	0.63
vs. Timolol	Brinzolamide	3	1.19	0.59	1.79	0.00	0%	1.05	-0.06	2.15
	Dorzolamide	5	0.91	0.29	1.54	0.23	46%	0.92	0.15	1.69
	Bimatoprost	6	-1.98	-2.42	-1.55	0.06	21%	-2.13	-2.85	-1.42
	Latanoprost	13	-1.29	-1.76	-0.82	0.42	66%	-1.30	-1.79	-0.81
	Travoprost	4	-0.80	-1.36	-0.24	0.00	0%	-0.72	-1.67	0.23
	Tafluprost	2	-0.93	-2.29	0.44	0.83	85%	-0.88	-1.98	0.21
	Unoprostone	2	0.94	-0.43	2.31	0.85	87%	0.96	-0.12	2.05
vs. Brinzolamide	Dorzolamide	2	-0.20	-0.82	0.41	0.00	0%	-0.24	-1.39	0.92
vs. Dorzolamide	Latanoprost	1	-2.90	-3.70	-2.10	NA	NA	-2.90	-4.49	-1.31
vs. Bimatoprost	Latanoprost	7	0.92	0.14	1.69	0.72	71%	0.90	0.22	1.59
	Travoprost	9	0.59	-0.06	1.25	0.65	70%	0.60	-0.01	1.20
vs. Latanoprost	Travoprost	7	-0.04	-0.49	0.41	0.00	0%	-0.06	-0.77	0.66
	Tafluprost	1	-0.90	-3.40	1.60	NA	NA	-0.90	-3.78	1.98
	Unoprostone	6	3.07	2.51	3.63	0.01	2%	2.95	2.13	3.78

Legend:
1. NA: Not applicable
2. There are 95 two-arm trials,12 three-arm trials
3. Mean difference is calucated using the IOP of the drug in column2-column1
4. Tau square: between-study variance in random-effect models; I square: proportion of variance due to heterogeneity
5. Glaucoma drugs are expected to lower IOP; therefore, mean difference >0 favors the drug in column 1, and mean difference <0 favors the drug in column 2.

6. *Estimated tau square is 0.4729; estimated I square is 64.34%
7.Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 10.3. Summary estimates of mean difference in IOP at 3 months derived from pairwise meta-analysis (FDA trials)

Column1	Column2	No. of studies	Comparison-Specific Heterogeneity					Common heterogeneity*		
			Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared	Mean difference	95% CI, lower	95% CI, upper
vs. Placebo/Vehicle/ No treatment	Betaxolol	1	-1.00	-2.19	0.20	NA	NA	-1.00	-2.42	0.42
	Timolol	1	-2.70	-3.87	-1.53	NA	NA	-2.70	-4.09	-1.31
	Levobetaxolol	1	-3.00	-4.53	-1.47	NA	NA	-3.00	-4.81	-1.19
vs. Betaxolol	Timolol	1	-1.70	-2.88	-0.52	NA	NA	-1.70	-3.11	-0.29
	Levobetaxolol	1	-2.00	-3.54	-0.46	NA	NA	-2.00	-3.82	-0.18
vs. Timolol	Levobetaxolol	3	1.25	0.27	2.23	0.52	73%	1.49	0.92	2.05
	Dorzolamide	4	1.61	0.93	2.29	0.06	12%	1.62	0.87	2.37
	Bimatoprost	2	-2.26	-2.82	-1.70	0.00	0%	-2.26	-2.93	-1.58
	Latanoprost	1	-1.10	-1.69	-0.51	NA	NA	-1.10	-1.82	-0.38
	Travoprost	3	-0.98	-1.45	-0.52	0.03	19%	-0.98	-1.48	-0.48
	Unoprostone	2	2.00	1.59	2.41	0.00	0%	2.00	1.50	2.50
vs. Brinzolamide	Dorzolamide	2	0.32	-0.17	0.80	NA	NA	0.31	-0.27	0.90
vs. Latanoprost	Travoprost	1	-0.30	-1.03	0.43	NA	NA	-0.30	-1.18	0.58

Legend:
1. NA: Not applicable
2. There are 14 two-arm trials,1 three-arm trial, and 1 four-arm trial
3. Mean difference is calculated using the IOP of the drug in column2-column1
4. Tau square: between-study variance in random-effect models; I square: proportion of variance due to heterogeneity
5. Glaucoma drugs are expected to lower IOP; therefore, mean difference >0 favors the drug in column 1, and mean difference <0 favors the drug in column 2.
6. *Estimated tau square is 0.0071; estimated I square is 29.99%
7.Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist

Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 10.4. Summary estimates of mean difference in IOP at 3 months derived from pairwise meta-analysis (ClincalTrials.gov trials)

Column1	Column2	No. of studies	Comparison-Specific Heterogeneity					Common heterogeneity*		
			Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared	Mean difference	95% CI, lower	95% CI, upper
vs. Brimonidine	Brinzolamide	4	-1.09	-1.92	-0.26	0.51	73%	-1.10	-2.03	-0.17
vs. Timolol	Travoprost	1	-1.80	-3.55	-0.05	NA	NA	-1.80	-4.19	0.59
	Tafluprost	2	-0.75	-2.51	1.01	1.46	90%	-0.70	-1.97	0.57
vs. Brinzolamide	Travoprost	1	-2.70	-3.99	-1.41	NA	NA	-2.70	-4.78	-0.62
vs. Bimatoprost	Travoprost	1	-0.14	-1.56	1.28	NA	NA	-0.14	-2.30	2.02

Legend:
1. NA: Not applicable
2. There are 9 two-arm trials
3. Mean difference is calucated using the IOP of the drug in column2-column1
4. Tau square: between-study variance in random-effect models; I square: proportion of variance due to heterogeneity
5. Glaucoma drugs are expected to lower IOP; therefore, mean difference >0 favors the drug in column 1, and mean difference <0 favors the drug in column 2.
6. *Estimated tau square is 0.6926; estimated I square is 81.30%
7.Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 10.5. Summary estimates of mean difference in IOP at 3 months derived from pairwise meta-analysis (Published trials not found on FDA or ClinicalTrials.gov)

Column1	Column2	No. of studies	Comparison-Specific Heterogeneity					Common heterogeneity*		
			Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared	Mean difference	95% CI, lower	95% CI, upper
vs. Placebo/Vehicle /No treatment	Brimonidine	1	-2.30	-3.99	-0.61	NA	NA	-2.30	-4.52	-0.08
	Betaxolol	2	-2.90	-4.65	-1.15	1.30	81%	-2.80	-4.04	-1.56
	Levobunolol	2	-7.51	-8.53	-6.50	0.00	0%	-7.44	-8.94	-5.94
	Timolol	4	-3.90	-5.12	-2.69	0.85	56%	-3.89	-4.97	-2.81
	Brinzolamide	1	-2.28	-4.04	-0.52	NA	NA	-2.28	-4.56	0.00
	Dorzolamide	3	-1.33	-1.68	-0.98	0.00	0%	-1.58	-2.77	-0.38
	Bimatoprost	1	-4.60	-5.60	-3.60	NA	NA	-4.60	-6.34	-2.86
	Unoprostone	1	-0.50	-1.70	0.70	NA	NA	-0.50	-2.36	1.36
vs. Apraclonidine	Timolol	2	-1.76	-3.27	-0.26	0.45	28%	-1.75	-3.32	-0.18
vs. Brimonidine	Betaxolol	1	-0.04	-1.03	0.95	NA	NA	-0.04	-1.77	1.69
	Timolol	4	-0.75	-2.15	0.66	1.72	94%	-0.76	-1.59	0.08
	Latanoprost	5	-1.08	-2.12	-0.05	1.13	83%	-1.15	-1.93	-0.38
	Travoprost	1	-1.20	-3.77	1.37	NA	NA	-1.20	-4.17	1.77
vs. Betaxolol	Levobunolol	2	-4.73	-10.01	0.55	12.25	83%	-3.34	-5.20	-1.47
	Timolol	7	-1.73	-2.60	-0.85	0.60	48%	-1.72	-2.56	-0.87
	Dorzolamide	2	-0.30	-0.96	0.36	0.00	0%	-0.35	-1.56	0.87
	Latanoprost	2	-1.05	-2.62	0.51	0.33	25%	-1.05	-2.75	0.65
vs. Carteolol	Levobunolol	1	-2.90	-4.59	-1.22	NA	NA	-2.90	-5.12	-0.68
	Timolol	4	0.03	-0.61	0.68	0.11	24%	0.06	-0.87	0.99
vs. Levobunolol	Timolol	11	-0.03	-0.44	0.39	0.01	3%	-0.01	-0.65	0.64
vs. Timolol	Brinzolamide	2	0.78	-1.04	2.61	1.00	41%	0.93	-0.52	2.39

Column1	Column2	No. of studies	Comparison-Specific Heterogeneity					Common heterogeneity*		
			Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared	Mean difference	95% CI, lower	95% CI, upper
	Dorzolamide	2	0.65	-0.43	1.73	0.41	68%	0.65	-0.52	1.82
	Bimatoprost	5	-2.08	-2.66	-1.50	0.15	36%	-2.20	-3.01	-1.39
	Latanoprost	13	-1.29	-1.76	-0.82	0.42	66%	-1.30	-1.81	-0.80
	Travoprost	3	-0.56	-1.39	0.27	0.00	0%	-0.55	-1.77	0.66
	Unoprostone	1	0.20	-0.63	1.03	NA	NA	0.20	-1.44	1.84
vs. Dorzolamide	Latanoprost	1	-2.90	-3.70	-2.10	NA	NA	-2.90	-4.52	-1.28
vs. Bimatoprost	Latanoprost	7	0.92	0.14	1.69	0.72	71%	0.90	0.20	1.60
	Travoprost	9	0.59	-0.06	1.25	0.65	70%	0.60	-0.02	1.21
vs. Latanoprost	Travoprost	7	-0.04	-0.49	0.41	0.00	0%	-0.05	-0.79	0.68
	Tafluprost	1	-0.90	-3.40	1.60	NA	NA	-0.90	-3.81	2.01
	Unoprostone	6	3.07	2.51	3.63	0.01	2%	2.95	2.11	3.79

Legend:
1. NA: Not applicable
2. There are 87 two-arm trials,9 three-arm trials
3. Mean difference is calculated using the IOP of the drug in column2-column1
4. Tau square: between-study variance in random-effect models; I square: proportion of variance due to heterogeneity
5. Glaucoma drugs are expected to lower IOP; therefore, mean difference >0 favors the drug in column 1, and mean difference <0 favors the drug in column 2.
6. *Estimated tau square is 0.4648; estimated I square is 64.17%
7.Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 11. Trial information for network meta-analyses

Evidence source	No. of trials	No. of participants	No. of interventions	No. of two-arm study (%)	No. of three-arm study (%)	No. of four-arm study (%)	No. of direct comparisons	No. of direct comparison based on 1 trial (%)	No. of direct comparison based on 2 trials (%)	Median number of trials for each direct comparison (IQR)	Most often used comparator (No. of trials, %)
All unique trials	121	20981	15	110(91%)	10(8%)	1(1%)	39	12(31%)	8(21%)	2(1-5.5)	Timolol (71,59%)
Published trials	107	17343	14	95(89%)	12(11%)	0	36	9(25%)	11(31%)	2(1.75-5)	Timolol (62,58%)
FDA trials	16	5250	10	14(88%)	1(6%)	1(6%)	13	7(54%)	3(23%)	1(1-2)	Timolol (14,88%)
ClinicalTrials.gov trials	9	2296	6	9(100%)	0	0	5	3(60%)	1(20%)	1(1-2)	Travoprost (3,60%)

Table 12.1. Summary estimates of mean difference in IOP at 3 months derived from NMA (all unique trials)

Bimatoprost	Travoprost	Tafluprost	Latanoprost	Levobunolol	Timolol	Carteolol	Brimonidine	Brinzolamide	Levobetaxolol	Dorzolamide	Betaxolol	Apraclonidine	Unoprostone	Placebo
Bimatoprost	0.69 (0.19,1.19)	0.83 (-0.38,2.03)	0.88 (0.38,1.38)	1.05 (0.31,1.79)	1.87 (1.40,2.34)	2.14 (1.12,3.15)	2.60 (1.93,3.27)	2.68 (1.90,3.47)	3.06 (1.95,4.17)	3.27 (2.56,3.98)	3.32 (2.61,4.03)	3.59 (1.90,5.29)	3.73 (2.97,4.49)	5.60 (4.90,6.29)
-0.69 (-1.19,-0.19)	Travoprost	0.13 (-1.07,1.33)	0.19 (-0.31,0.68)	0.36 (-0.39,1.11)	1.18 (0.70,1.66)	1.44 (0.43,2.46)	1.90 (1.24,2.57)	1.99 (1.22,2.76)	2.37 (1.26,3.48)	2.58 (1.87,3.29)	2.63 (1.91,3.35)	2.90 (1.20,4.59)	3.04 (2.28,3.80)	4.90 (4.19,5.61)
-0.83 (-2.03,0.38)	-0.13 (-1.33,1.07)	Tafluprost	0.05 (-1.10,1.21)	0.22 (-1.03,1.48)	1.04 (-0.07,2.16)	1.31 (-0.12,2.74)	1.77 (0.55,3.00)	1.86 (0.56,3.15)	2.24 (0.74,3.73)	2.44 (1.20,3.68)	2.50 (1.25,3.74)	2.77 (0.80,4.73)	2.91 (1.63,4.19)	4.77 (3.53,6.01)
-0.88 (-1.38,-0.38)	-0.19 (-0.68,0.31)	-0.05 (-1.21,1.10)	Latanoprost	0.17 (-0.51,0.85)	0.99 (0.63,1.36)	1.26 (0.29,2.22)	1.72 (1.17,2.27)	1.80 (1.09,2.51)	2.18 (1.12,3.25)	2.39 (1.76,3.02)	2.44 (1.81,3.07)	2.71 (1.05,4.38)	2.85 (2.21,3.50)	4.72 (4.09,5.34)
-1.05 (-1.79,-0.31)	-0.36 (-1.11,0.39)	-0.22 (-1.48,1.03)	-0.17 (-0.85,0.51)	Levobunolol	0.82 (0.24,1.40)	1.09 (0.07,2.11)	1.55 (0.77,2.33)	1.63 (0.76,2.51)	2.01 (0.86,3.17)	2.22 (1.43,3.01)	2.27 (1.51,3.03)	2.54 (0.81,4.27)	2.68 (1.82,3.54)	4.54 (3.80,5.29)
-1.87 (-2.34,-1.40)	-1.18 (-1.66,-0.70)	-1.04 (-2.16,0.07)	-0.99 (-1.36,-0.63)	-0.82 (-1.40,-0.24)	Timolol	0.27 (-0.63,1.16)	0.73 (0.19,1.26)	0.81 (0.14,1.48)	1.19 (0.19,2.20)	1.40 (0.84,1.96)	1.45 (0.89,2.02)	1.72 (0.10,3.35)	1.86 (1.22,2.51)	3.73 (3.17,4.28)
-2.14 (-3.15,-1.12)	-1.44 (-2.46,-0.43)	-1.31 (-2.74,0.12)	-1.26 (-2.22,-0.29)	-1.09 (-2.11,-0.07)	-0.27 (-1.16,0.63)	Carteolol	0.46 (-0.58,1.50)	0.55 (-0.57,1.67)	0.93 (-0.42,2.27)	1.13 (0.08,2.19)	1.19 (0.13,2.24)	1.46 (-0.40,3.31)	1.60 (0.49,2.70)	3.46 (2.41,4.51)
-2.60 (-3.27,-1.93)	-1.90 (-2.57,-1.24)	-1.77 (-3.00,-0.55)	-1.72 (-2.27,-1.17)	-1.55 (-2.33,-0.77)	-0.73 (-1.26,-0.19)	-0.46 (-1.50,0.58)	Brimonidine	0.09 (-0.58,0.75)	0.46 (-0.67,1.59)	0.67 (-0.04,1.38)	0.73 (0.01,1.44)	1.00 (-0.72,2.71)	1.14 (0.34,1.93)	3.00 (2.28,3.71)
-2.68 (-3.47,-1.90)	-1.99 (-2.76,-1.22)	-1.86 (-3.15,-0.56)	-1.80 (-2.51,-1.09)	-1.63 (-2.51,-0.76)	-0.81 (-1.48,-0.14)	-0.55 (-1.67,0.57)	-0.09 (-0.75,0.58)	Brinzolamide	0.38 (-0.82,1.58)	0.59 (-0.16,1.33)	0.64 (-0.18,1.47)	0.91 (-0.85,2.67)	1.05 (0.15,1.96)	2.91 (2.11,3.71)
-3.06 (-4.17,-1.95)	-2.37 (-3.48,-1.26)	-2.24 (-3.73,-0.74)	-2.18 (-3.25,-1.12)	-2.01 (-3.17,-0.86)	-1.19 (-2.20,-0.19)	-0.93 (-2.27,0.42)	-0.46 (-1.59,0.67)	-0.38 (-1.58,0.82)	Levobetaxolol	0.21 (-0.93,1.35)	0.26 (-0.86,1.38)	0.53 (-1.38,2.44)	0.67 (-0.52,1.86)	2.53 (1.42,3.65)
-3.27 (-3.98,-2.56)	-2.58 (-3.29,-1.87)	-2.44 (-3.68,-1.20)	-2.39 (-3.02,-1.76)	-2.22 (-3.01,-1.43)	-1.40 (-1.96,-0.84)	-1.13 (-2.19,-0.08)	-0.67 (-1.38,0.04)	-0.59 (-1.33,0.16)	-0.21 (-1.35,0.93)	Dorzolamide	0.05 (-0.65,0.75)	0.32 (-1.40,2.04)	0.46 (-0.36,1.29)	2.33 (1.64,3.01)
-3.32 (-4.03,-2.61)	-2.63 (-3.35,-1.91)	-2.50 (-3.74,-1.25)	-2.44 (-3.07,-1.81)	-2.27 (-3.03,-1.51)	-1.45 (-2.02,-0.89)	-1.19 (-2.24,-0.13)	-0.73 (-1.44,-0.01)	-0.64 (-1.47,0.18)	-0.26 (-1.38,0.86)	-0.05 (-0.75,0.65)	Betaxolol	0.27 (-1.45,1.99)	0.41 (-0.42,1.24)	2.27 (1.60,2.95)
-3.59 (-5.29,-1.90)	-2.90 (-4.59,-1.20)	-2.77 (-4.73,-0.80)	-2.71 (-4.38,-1.05)	-2.54 (-4.27,-0.81)	-1.72 (-3.35,-0.10)	-1.46 (-3.31,0.40)	-1.00 (-2.71,0.72)	-0.91 (-2.67,0.85)	-0.53 (-2.44,1.38)	-0.32 (-2.04,1.40)	-0.27 (-1.99,1.45)	Apraclonidine	0.14 (-1.61,1.89)	2.00 (0.28,3.72)
-3.73 (-4.49,-2.97)	-3.04 (-3.80,-2.28)	-2.91 (-4.19,-1.63)	-2.85 (-3.50,-2.21)	-2.68 (-3.54,-1.82)	-1.86 (-2.51,-1.22)	-1.60 (-2.70,-0.49)	-1.14 (-1.93,-0.34)	-1.05 (-1.96,-0.15)	-0.67 (-1.86,0.52)	-0.46 (-1.29,0.36)	-0.41 (-1.24,0.42)	-0.14 (-1.89,1.61)	Unoprostone	1.86 (1.06,2.66)
-5.60 (-6.29,-4.90)	-4.90 (-5.61,-4.19)	-4.77 (-6.01,-3.53)	-4.72 (-5.34,-4.09)	-4.54 (-5.29,-3.80)	-3.73 (-4.28,-3.17)	-3.46 (-4.51,-2.41)	-3.00 (-3.71,-2.28)	-2.91 (-3.71,-2.11)	-2.53 (-3.65,-1.42)	-2.33 (-3.01,-1.64)	-2.27 (-2.95,-1.60)	-2.00 (-3.72,-0.28)	-1.86 (-2.66,-1.06)	Placebo

Legend:

1. Glaucoma drugs are expected to lower IOP; therefore, mean difference <0 favors the drug in the column, and mean difference >0 favors the drug in the row.
2. Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 12.2 Summary estimates of mean difference in IOP at 3 months derived from NMA (published trials)

Bimatoprost	Travoprost	Tafluprost	Latanoprost	Levobunolol	Timolol	Carteolol	Brimonidine	Brinzolamide	Dorzolamide	Betaxolol	Apraclonidine	Unoprostone	Placebo
Bimatoprost	0.75 (0.18,1.31)	0.77 (-0.48,2.02)	0.82 (0.29,1.36)	0.98 (0.19,1.77)	1.83 (1.30,2.36)	2.09 (1.03,3.15)	2.46 (1.74,3.19)	2.95 (2.04,3.85)	3.08 (2.30,3.86)	3.09 (2.35,3.84)	3.54 (1.79,5.28)	3.62 (2.79,4.44)	5.52 (4.78,6.26)
-0.75 (-1.31,-0.18)	Travoprost	0.02 (-1.26,1.30)	0.07 (-0.50,0.65)	0.23 (-0.60,1.06)	1.08 (0.49,1.66)	1.34 (0.25,2.44)	1.72 (0.96,2.48)	2.20 (1.26,3.14)	2.33 (1.51,3.15)	2.35 (1.56,3.13)	2.79 (1.02,4.55)	2.87 (2.01,3.73)	4.77 (3.98,5.57)
-0.77 (-2.02,0.48)	-0.02 (-1.30,1.26)	Tafluprost	0.05 (-1.14,1.25)	0.21 (-1.08,1.50)	1.06 (-0.09,2.21)	1.32 (-0.15,2.80)	1.69 (0.42,2.97)	2.18 (0.80,3.55)	2.31 (1.02,3.61)	2.32 (1.05,3.60)	2.77 (0.75,4.79)	2.85 (1.51,4.18)	4.75 (3.46,6.04)
-0.82 (-1.36,-0.29)	-0.07 (-0.65,0.50)	-0.05 (-1.25,1.14)	Latanoprost	0.16 (-0.55,0.87)	1.01 (0.61,1.40)	1.27 (0.27,2.27)	1.64 (1.06,2.22)	2.12 (1.30,2.94)	2.26 (1.58,2.94)	2.27 (1.63,2.91)	2.71 (1.00,4.43)	2.79 (2.11,3.48)	4.70 (4.04,5.36)
-0.98 (-1.77,-0.19)	-0.23 (-1.06,0.60)	-0.21 (-1.50,1.08)	-0.16 (-0.87,0.55)	Levobunolol	0.85 (0.25,1.44)	1.11 (0.06,2.16)	1.48 (0.67,2.29)	1.97 (1.01,2.92)	2.10 (1.27,2.93)	2.11 (1.33,2.89)	2.56 (0.79,4.32)	2.63 (1.72,3.55)	4.54 (3.76,5.31)
-1.83 (-2.36,-1.30)	-1.08 (-1.66,-0.49)	-1.06 (-2.21,0.09)	-1.01 (-1.40,-0.61)	-0.85 (-1.44,-0.25)	Timolol	0.27 (-0.66,1.19)	0.64 (0.07,1.21)	1.12 (0.35,1.89)	1.25 (0.64,1.87)	1.27 (0.70,1.84)	1.71 (0.04,3.37)	1.79 (1.08,2.50)	3.69 (3.10,4.28)
-2.09 (-3.15,-1.03)	-1.34 (-2.44,-0.25)	-1.32 (-2.80,0.15)	-1.27 (-2.27,-0.27)	-1.11 (-2.16,-0.06)	-0.27 (-1.19,0.66)	Carteolol	0.37 (-0.71,1.45)	0.85 (-0.34,2.05)	0.99 (-0.11,2.09)	1.00 (-0.08,2.08)	1.44 (-0.46,3.35)	1.52 (0.36,2.68)	3.43 (2.34,4.51)
-2.46 (-3.19,-1.74)	-1.72 (-2.48,-0.96)	-1.69 (-2.97,-0.42)	-1.64 (-2.22,-1.06)	-1.48 (-2.29,-0.67)	-0.64 (-1.21,-0.07)	-0.37 (-1.45,0.71)	Brimonidine	0.48 (-0.34,1.30)	0.62 (-0.16,1.40)	0.63 (-0.11,1.37)	1.07 (-0.69,2.83)	1.15 (0.30,2.00)	3.05 (2.30,3.81)
-2.95 (-3.85,-2.04)	-2.20 (-3.14,-1.26)	-2.18 (-3.55,-0.80)	-2.12 (-2.94,-1.30)	-1.97 (-2.92,-1.01)	-1.12 (-1.89,-0.35)	-0.85 (-2.05,0.34)	-0.48 (-1.30,0.34)	Brinzolamide	0.13 (-0.72,0.99)	0.15 (-0.76,1.05)	0.59 (-1.24,2.42)	0.67 (-0.34,1.68)	2.57 (1.72,3.43)
-3.08 (-3.86,-2.30)	-2.33 (-3.15,-1.51)	-2.31 (-3.61,-1.02)	-2.26 (-2.94,-1.58)	-2.10 (-2.93,-1.27)	-1.25 (-1.87,-0.64)	-0.99 (-2.09,0.11)	-0.62 (-1.40,0.16)	-0.13 (-0.99,0.72)	Dorzolamide	0.01 (-0.72,0.75)	0.46 (-1.32,2.23)	0.53 (-0.36,1.43)	2.44 (1.73,3.14)
-3.09 (-3.84,-2.35)	-2.35 (-3.13,-1.56)	-2.32 (-3.60,-1.05)	-2.27 (-2.91,-1.63)	-2.11 (-2.89,-1.33)	-1.27 (-1.84,-0.70)	-1.00 (-2.08,0.08)	-0.63 (-1.37,0.11)	-0.15 (-1.05,0.76)	-0.01 (-0.75,0.72)	Betaxolol	0.44 (-1.32,2.20)	0.52 (-0.31,1.36)	2.42 (1.72,3.13)
-3.54 (-5.28,-1.79)	-2.79 (-4.55,-1.02)	-2.77 (-4.79,-0.75)	-2.71 (-4.43,-1.00)	-2.56 (-4.32,-0.79)	-1.71 (-3.37,-0.04)	-1.44 (-3.35,0.46)	-1.07 (-2.83,0.69)	-0.59 (-2.42,1.24)	-0.46 (-2.23,1.32)	-0.44 (-2.20,1.32)	Apraclonidine	0.08 (-1.73,1.89)	1.98 (0.21,3.75)
-3.62 (-4.44,-2.79)	-2.87 (-3.73,-2.01)	-2.85 (-4.18,-1.51)	-2.79 (-3.48,-2.11)	-2.63 (-3.55,-1.72)	-1.79 (-2.50,-1.08)	-1.52 (-2.68,-0.36)	-1.15 (-2.00,-0.30)	-0.67 (-1.68,0.34)	-0.53 (-1.43,0.36)	-0.52 (-1.36,0.31)	-0.08 (-1.89,1.73)	Unoprostone	1.90 (1.06,2.75)
-5.52 (-6.26,-4.78)	-4.77 (-5.57,-3.98)	-4.75 (-6.04,-3.46)	-4.70 (-5.36,-4.04)	-4.54 (-5.31,-3.76)	-3.69 (-4.28,-3.10)	-3.43 (-4.51,-2.34)	-3.05 (-3.81,-2.30)	-2.57 (-3.43,-1.72)	-2.44 (-3.14,-1.73)	-2.42 (-3.13,-1.72)	-1.98 (-3.75,-0.21)	-1.90 (-2.75,-1.06)	Placebo

Legend:

1. Glaucoma drugs are expected to lower IOP; therefore, mean difference <0 favors the drug in the column, and mean difference >0 favors the drug in the row.
2. Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 12.3. Summary estimates of mean difference in IOP at 3 months derived from NMA (FDA trials)

Bimatoprost	Travoprost	Latanoprost	Timolol	Brinzolamide	Levobetaxolol	Dorzolamide	Unoprostone	Betaxolol	Placebo
Bimatoprost	1.28 (0.56,1.99)	1.30 (0.48,2.12)	2.26 (1.69,2.83)	3.57 (2.57,4.56)	3.75 (2.98,4.51)	3.88 (3.02,4.74)	4.26 (3.54,4.97)	4.48 (3.22,5.74)	5.48 (4.24,6.72)
-1.28 (-1.99,-0.56)	Travoprost	0.02 (-0.61,0.66)	0.98 (0.55,1.41)	2.29 (1.37,3.20)	2.47 (1.81,3.13)	2.60 (1.83,3.37)	2.98 (2.38,3.59)	3.20 (2.00,4.40)	4.20 (3.02,5.39)
-1.30 (-2.12,-0.48)	-0.02 (-0.66,0.61)	Latanoprost	0.96 (0.38,1.54)	2.27 (1.27,3.26)	2.45 (1.66,3.24)	2.58 (1.71,3.45)	2.96 (2.23,3.69)	3.18 (1.92,4.44)	4.18 (2.94,5.42)
-2.26 (-2.83,-1.69)	-0.98 (-1.41,-0.55)	-0.96 (-1.54,-0.38)	Timolol	1.31 (0.50,2.12)	1.49 (0.98,2.00)	1.62 (0.98,2.26)	2.00 (1.57,2.43)	2.22 (1.10,3.34)	3.22 (2.12,4.32)
-3.57 (-4.56,-2.57)	-2.29 (-3.20,-1.37)	-2.27 (-3.26,-1.27)	-1.31 (-2.12,-0.50)	Brinzolamide	0.18 (-0.77,1.14)	0.31 (-0.18,0.81)	0.69 (-0.22,1.61)	0.91 (-0.47,2.29)	1.91 (0.55,3.28)
-3.75 (-4.51,-2.98)	-2.47 (-3.13,-1.81)	-2.45 (-3.24,-1.66)	-1.49 (-2.00,-0.98)	-0.18 (-1.14,0.77)	Levobetaxolol	0.13 (-0.68,0.94)	0.51 (-0.14,1.17)	0.73 (-0.45,1.91)	1.73 (0.56,2.90)
-3.88 (-4.74,-3.02)	-2.60 (-3.37,-1.83)	-2.58 (-3.45,-1.71)	-1.62 (-2.26,-0.98)	-0.31 (-0.81,0.18)	-0.13 (-0.94,0.68)	Dorzolamide	0.38 (-0.39,1.15)	0.60 (-0.69,1.89)	1.60 (0.32,2.88)
-4.26 (-4.97,-3.54)	-2.98 (-3.59,-2.38)	-2.96 (-3.69,-2.23)	-2.00 (-2.43,-1.57)	-0.69 (-1.61,0.22)	-0.51 (-1.17,0.14)	-0.38 (-1.15,0.39)	Unoprostone	0.22 (-0.98,1.42)	1.22 (0.03,2.41)
-4.48 (-5.74,-3.22)	-3.20 (-4.40,-2.00)	-3.18 (-4.44,-1.92)	-2.22 (-3.34,-1.10)	-0.91 (-2.29,0.47)	-0.73 (-1.91,0.45)	-0.60 (-1.89,0.69)	-0.22 (-1.42,0.98)	Betaxolol	1.00 (-0.21,2.21)
-5.48 (-6.72,-4.24)	-4.20 (-5.39,-3.02)	-4.18 (-5.42,-2.94)	-3.22 (-4.32,-2.12)	-1.91 (-3.28,-0.55)	-1.73 (-2.90,-0.56)	-1.60 (-2.88,-0.32)	-1.22 (-2.41,-0.03)	-1.00 (-2.21,0.21)	Placebo

Legend:

1. Glaucoma drugs are expected to lower IOP; therefore, mean difference <0 favors the drug in the column, and mean difference >0 favors the drug in the row.
2. Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 12.4. Summary estimates of mean difference in IOP at 3 months derived from NMA (ClinicalTrials.gov trials)

Travoprost	Bimatoprost	Tafluprost	Timolol	Brinzolamide	Brimonidine
Travoprost	0.14 (-2.02,2.30)	1.10 (-1.61,3.81)	1.80 (-0.59,4.19)	2.70 (0.62,4.78)	3.80 (1.52,6.08)
-0.14 (-2.30,2.02)	Bimatoprost	0.96 (-2.51,4.43)	1.66 (-1.56,4.88)	2.56 (-0.44,5.56)	3.66 (0.52,6.80)
-1.10 (-3.81,1.61)	-0.96 (-4.43,2.51)	Tafluprost	0.70 (-0.58,1.98)	1.60 (-1.82,5.01)	2.70 (-0.85,6.24)
-1.80 (-4.19,0.59)	-1.66 (-4.88,1.56)	-0.70 (-1.98,0.58)	Timolol	0.90 (-2.27,4.07)	2.00 (-1.30,5.30)
-2.70 (-4.78,-0.62)	-2.56 (-5.56,0.44)	-1.60 (-5.01,1.82)	-0.90 (-4.07,2.27)	Brinzolamide	1.10 (0.17,2.03)
-3.80 (-6.08,-1.52)	-3.66 (-6.80,-0.52)	-2.70 (-6.24,0.85)	-2.00 (-5.30,1.30)	-1.10 (-2.03,-0.17)	Brimonidine

Legend:

1. Glaucoma drugs are expected to lower IOP; therefore, mean difference <0 favors the drug in the column, and mean difference >0 favors the drug in the row.
2. Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 12.5. Summary estimates of mean difference in IOP at 3 months derived from NMA (published trials not found on FDA or ClinicalTrials.gov)

Tafluprost	Bimatoprost	Travoprost	Latanoprost	Levobunolol	Timolol	Carteolol	Brimonidine	Brinzolamide	Betaxolol
Tafluprost	0.09 (-2.99,3.17)	0.83 (-2.26,3.92)	0.90 (-2.13,3.93)	1.09 (-2.03,4.21)	1.92 (-1.14,4.98)	2.19 (-1.01,5.40)	2.46 (-0.64,5.55)	2.98 (-0.37,6.33)	3.25 (0.14,6.36)
-0.09 (-3.17,2.99)	Bimatoprost	0.74 (0.13,1.34)	0.81 (0.23,1.39)	1.00 (0.15,1.84)	1.83 (1.24,2.42)	2.10 (0.98,3.23)	2.37 (1.56,3.17)	2.89 (1.39,4.38)	3.16 (2.32,3.99)
-0.83 (-3.92,2.26)	-0.74 (-1.34,-0.13)	Travoprost	0.07 (-0.56,0.70)	0.26 (-0.63,1.16)	1.09 (0.44,1.75)	1.37 (0.20,2.53)	1.63 (0.79,2.47)	2.15 (0.63,3.68)	2.42 (1.54,3.31)
-0.90 (-3.93,2.13)	-0.81 (-1.39,-0.23)	-0.07 (-0.70,0.56)	Latanoprost	0.19 (-0.56,0.93)	1.02 (0.59,1.45)	1.29 (0.24,2.35)	1.56 (0.92,2.20)	2.08 (0.64,3.52)	2.35 (1.64,3.07)
-1.09 (-4.21,2.03)	-1.00 (-1.84,-0.15)	-0.26 (-1.16,0.63)	-0.19 (-0.93,0.56)	Levobunolol	0.83 (0.21,1.46)	1.10 (0.01,2.19)	1.37 (0.49,2.25)	1.89 (0.39,3.40)	2.16 (1.33,3.00)
-1.92 (-4.98,1.14)	-1.83 (-2.42,-1.24)	-1.09 (-1.75,-0.44)	-1.02 (-1.45,-0.59)	-0.83 (-1.46,-0.21)	Timolol	0.27 (-0.69,1.23)	0.54 (-0.11,1.18)	1.06 (-0.33,2.45)	1.33 (0.68,1.98)
-2.19 (-5.40,1.01)	-2.10 (-3.23,-0.98)	-1.37 (-2.53,-0.20)	-1.29 (-2.35,-0.24)	-1.10 (-2.19,-0.01)	-0.27 (-1.23,0.69)	Carteolol	0.26 (-0.89,1.42)	0.79 (-0.90,2.47)	1.06 (-0.09,2.21)
-2.46 (-5.55,0.64)	-2.37 (-3.17,-1.56)	-1.63 (-2.47,-0.79)	-1.56 (-2.20,-0.92)	-1.37 (-2.25,-0.49)	-0.54 (-1.18,0.11)	-0.26 (-1.42,0.89)	Brimonidine	0.52 (-0.99,2.04)	0.79 (-0.04,1.63)
-2.98 (-6.33,0.37)	-2.89 (-4.38,-1.39)	-2.15 (-3.68,-0.63)	-2.08 (-3.52,-0.64)	-1.89 (-3.40,-0.39)	-1.06 (-2.45,0.33)	-0.79 (-2.47,0.90)	-0.52 (-2.04,0.99)	Brinzolamide	0.27 (-1.24,1.77)
-3.25 (-6.36,-0.14)	-3.16 (-3.99,-2.32)	-2.42 (-3.31,-1.54)	-2.35 (-3.07,-1.64)	-2.16 (-3.00,-1.33)	-1.33 (-1.98,-0.68)	-1.06 (-2.21,0.09)	-0.79 (-1.63,0.04)	-0.27 (-1.77,1.24)	Betaxolol
-3.32 (-6.47,-0.17)	-3.23 (-4.20,-2.26)	-2.49 (-3.50,-1.48)	-2.42 (-3.28,-1.55)	-2.23 (-3.23,-1.23)	-1.40 (-2.22,-0.58)	-1.13 (-2.38,0.13)	-0.86 (-1.85,0.13)	-0.34 (-1.92,1.24)	-0.07 (-0.96,0.82)
-3.61 (-7.12,-0.10)	-3.52 (-5.34,-1.69)	-2.78 (-4.63,-0.94)	-2.71 (-4.49,-0.93)	-2.52 (-4.36,-0.69)	-1.69 (-3.42,0.04)	-1.42 (-3.39,0.56)	-1.15 (-3.00,0.69)	-0.63 (-2.84,1.58)	-0.36 (-2.20,1.48)
-3.73 (-6.85,-0.60)	-3.63 (-4.58,-2.69)	-2.90 (-3.88,-1.91)	-2.83 (-3.61,-2.04)	-2.64 (-3.67,-1.61)	-1.81 (-2.64,-0.97)	-1.53 (-2.81,-0.26)	-1.27 (-2.25,-0.28)	-0.75 (-2.35,0.86)	-0.48 (-1.49,0.54)
-5.73 (-8.84,-2.62)	-5.63 (-6.44,-4.82)	-4.90 (-5.77,-4.02)	-4.83 (-5.54,-4.11)	-4.64 (-5.46,-3.82)	-3.80 (-4.45,-3.16)	-3.53 (-4.68,-2.38)	-3.27 (-4.11,-2.42)	-2.74 (-4.19,-1.30)	-2.47 (-3.25,-1.70)

Legend:

1. Glaucoma drugs are expected to lower IOP; therefore, mean difference <0 favors the drug in the column, and mean difference >0 favors the drug in the row.
2. Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Table 13. SUCRA values and mean ranks generated by NMAs

Drugs	SUCRA value					Mean rank				
	Trials					Trials				
	All unique	Published	FDA	ClinicalTrials .gov	Published not in FDA/CT.gov	All unique	Published	FDA	ClinicalTrials .gov	Published not in FDA/CT.gov
Bimatoprost	99.3	99	100	79.1	95.8	1.1	1.1	1	2	1.6
Travoprost	86.8	83	83.6	85.1	81.3	2.8	3.2	2.5	1.7	3.4
Tafluprost	82.7	82.3		62	87.4	3.4	3.3		2.9	2.6
Latanoprost	81.3	81	83		79.8	3.6	3.5	2.5		3.6
Levobunolol	77.6	76.8			75.6	4.1	4			4.2
Timolol	62.2	59.4	66.7	39.1	59.1	6.3	6.3	4	4	6.3
Carteolol	56.6	52.8			51.8	7.1	7.1			7.3
Brimonidine	46.2	45.5		4.4	46.1	8.5	8.1		5.8	8
Brinzolamide	39.1	31.7	48.7	30.3	33.8	9.5	9.9	5.6	4.5	9.6
Levobetaxolol	33		42.2			10.4		6.2		
Dorzolamide	26.1	27.1	34.8		24.7	11.4	10.5	6.9		10.8
Betaxolol	24.7	27.3	18.8		27	11.5	10.4	8.3		10.5
Apraclonidine	20.8	20.2			21.7	12.1	11.4			11.2
Unoprostone	13.4	13.8	21.1		15.9	13.1	12.2	8.1		11.9
Placebo	0.1	0.1	1		0.1	15	14	9.9		14

Legend:
Color coding:

Green	Difference in relative rankings compared to all-unique trial network
White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

8. Figures

Figure 1.1. Identification of trials (bibliographic databases)

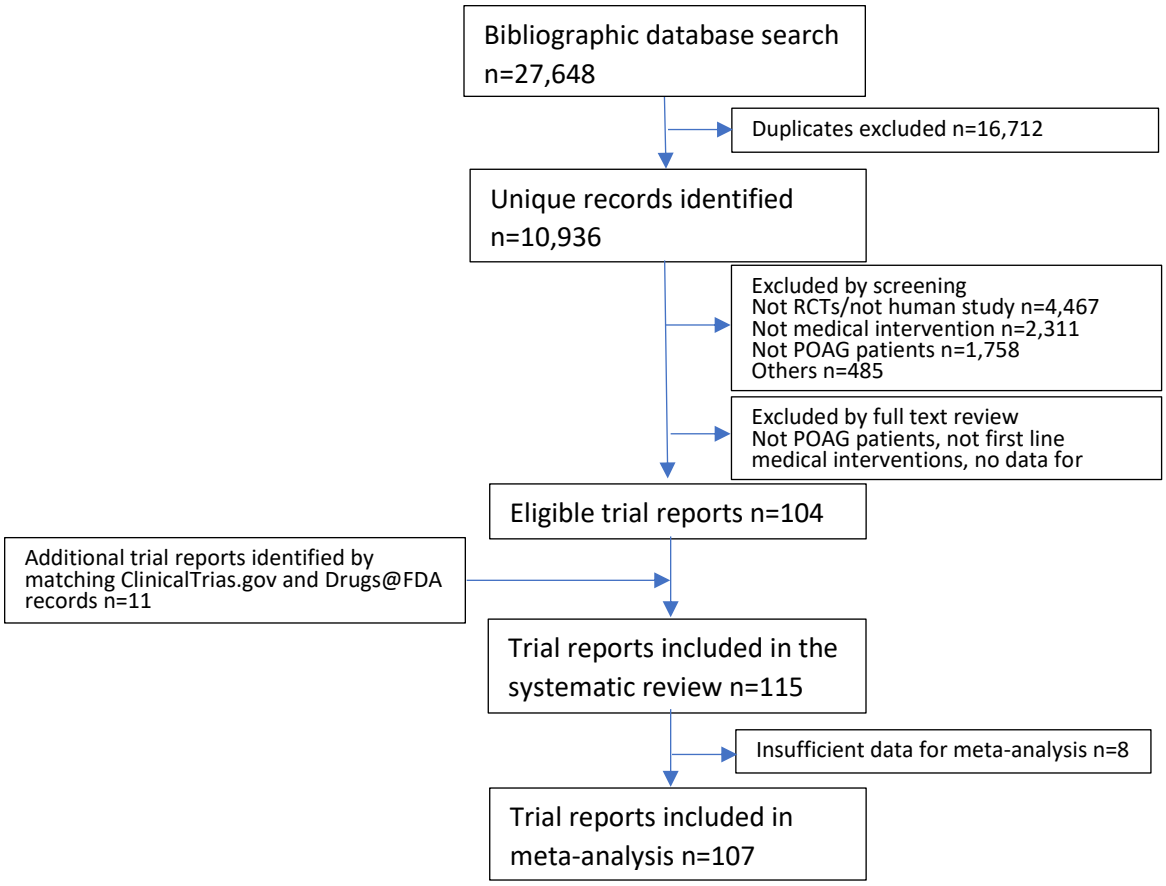


Figure 1.2. Identification of trials (Drugs@FDA)

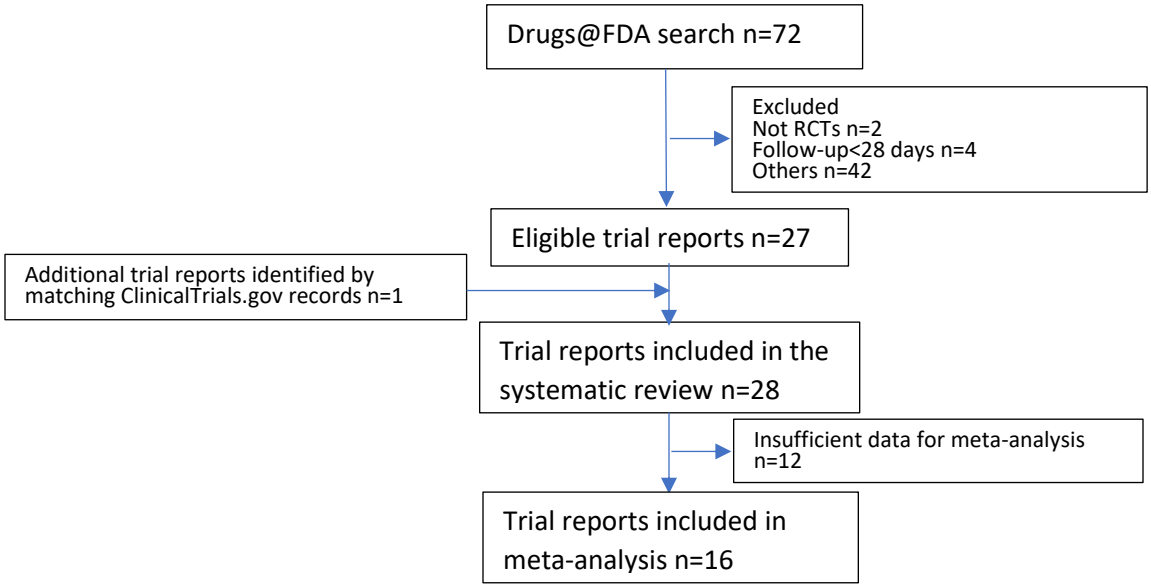


Figure 1.3. Identification of trials (ClinicalTrial.gov)

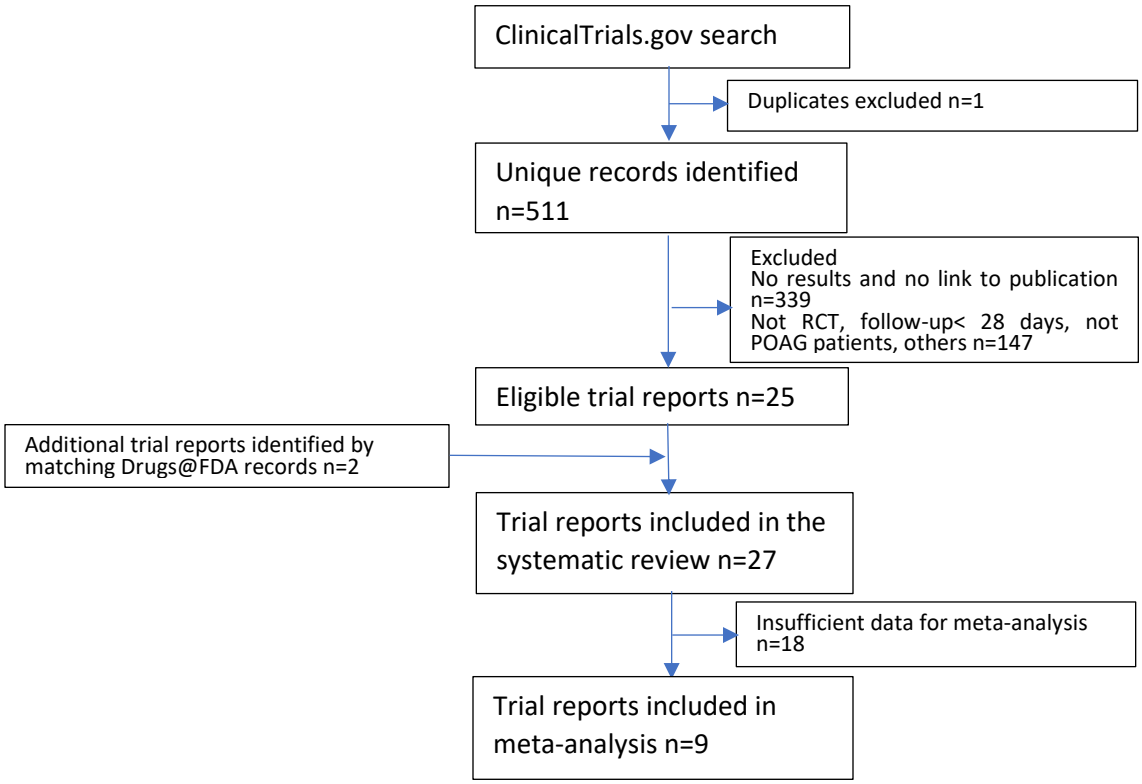
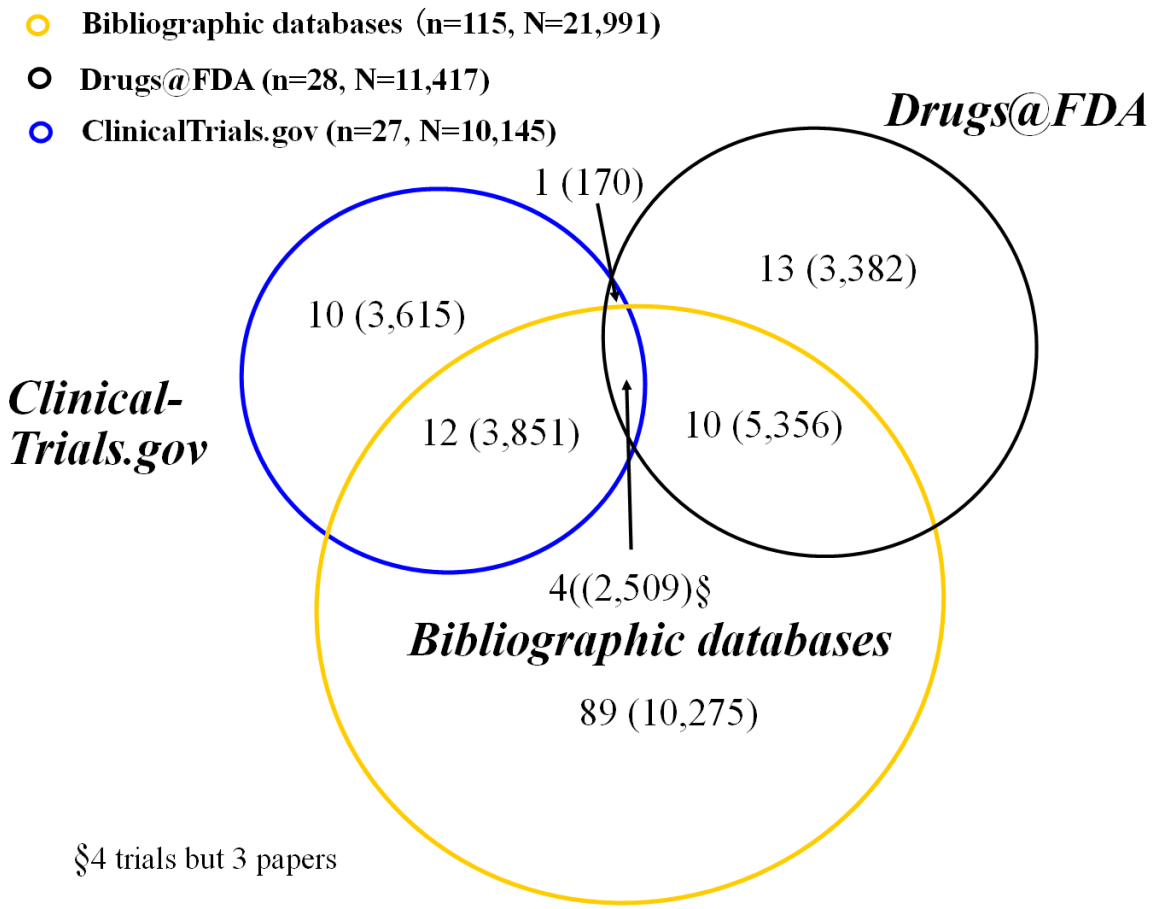
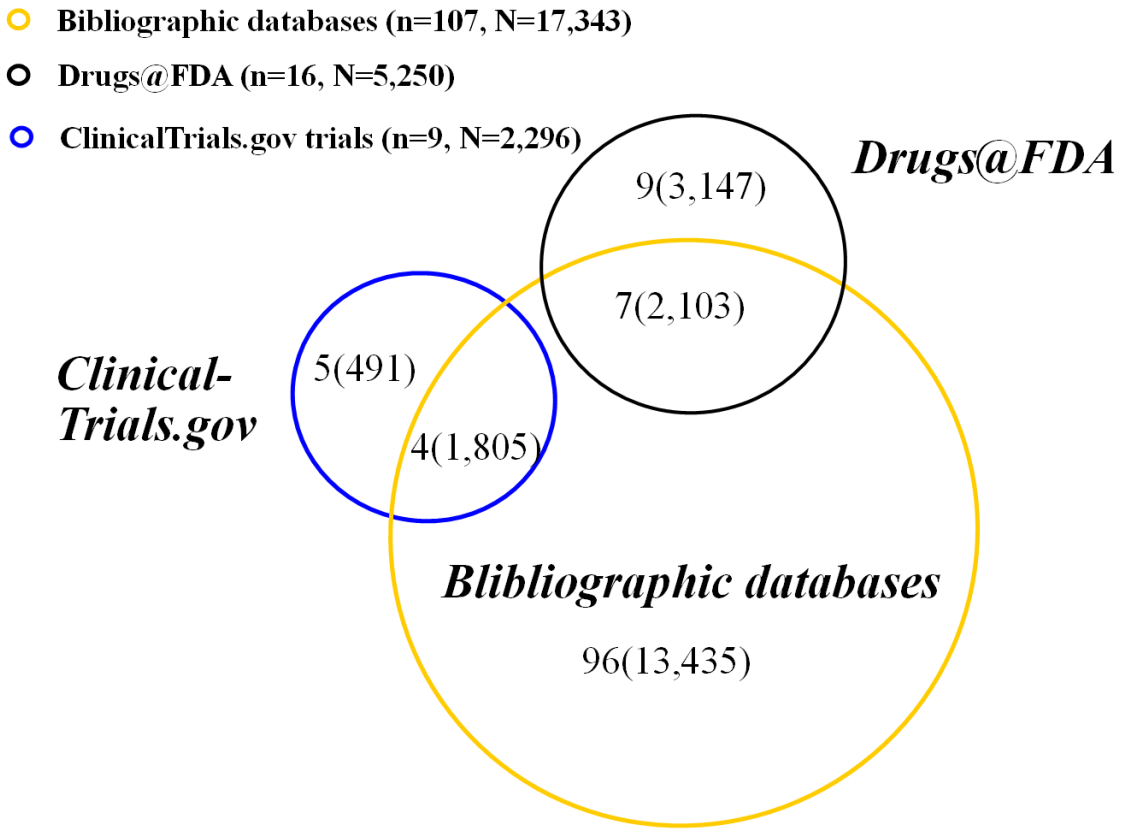


Figure 2.1. The extent of overlap of trials among bibliographic database, Drugs@FDA, and ClinicalTrials.gov (all trials)



Legend:
1. n: Number of trials
2. N: Number of participants
3. §: 4 trials but 3 papers

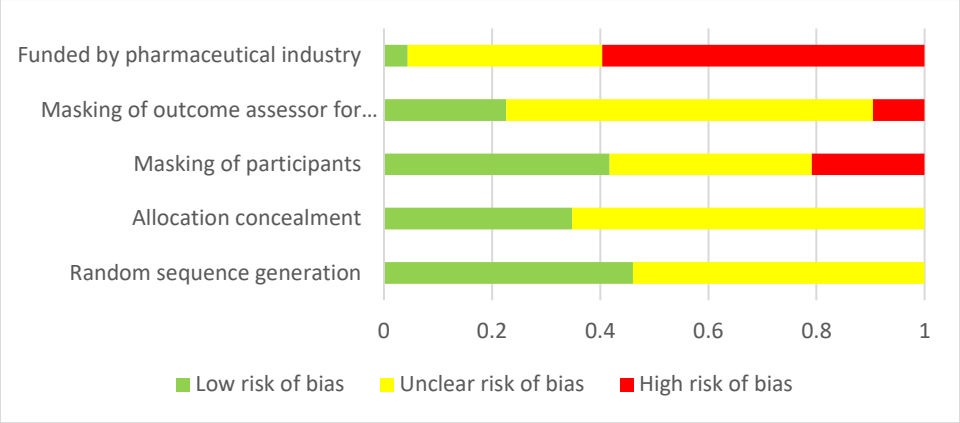
Figure 2.2. The extent of overlap of trials among bibliographic database, Drugs@FDA, and ClinicalTrials.gov (trials with sufficient data for NMA)



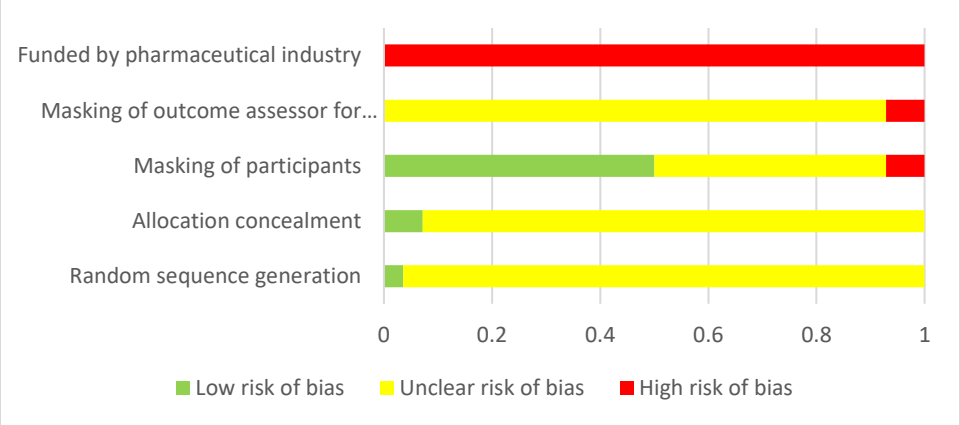
Legend:
1. n: Number of trials
2. N: Number of participants

Figure 3. Risk of bias assessment

Trials from bibliographic databases



Trials from Drugs@FDA



Trials from ClinicalTrials.gov

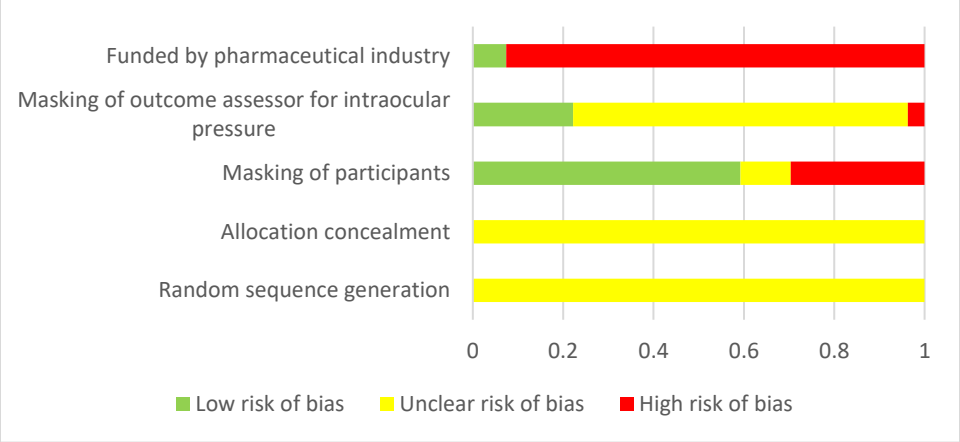
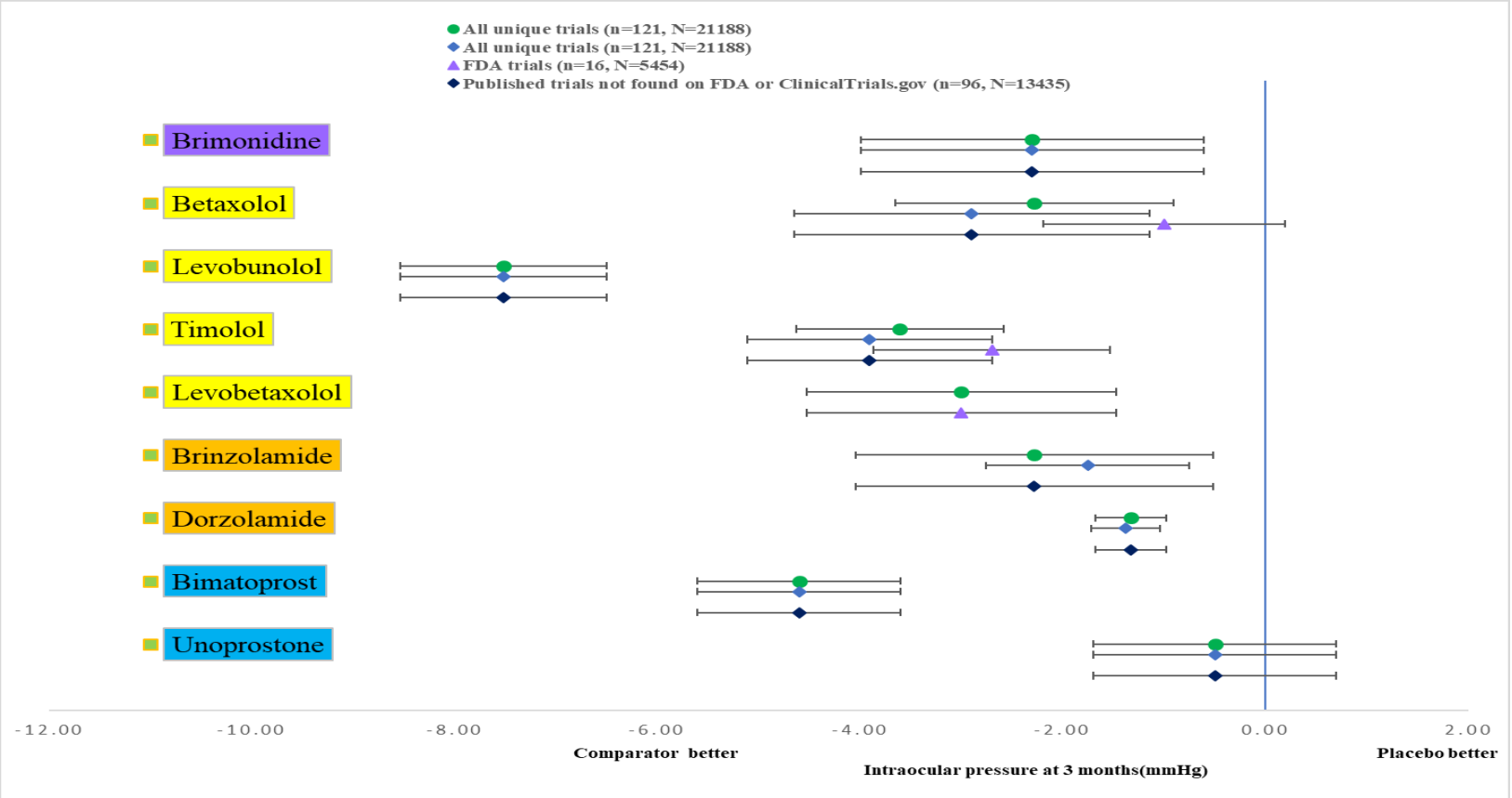


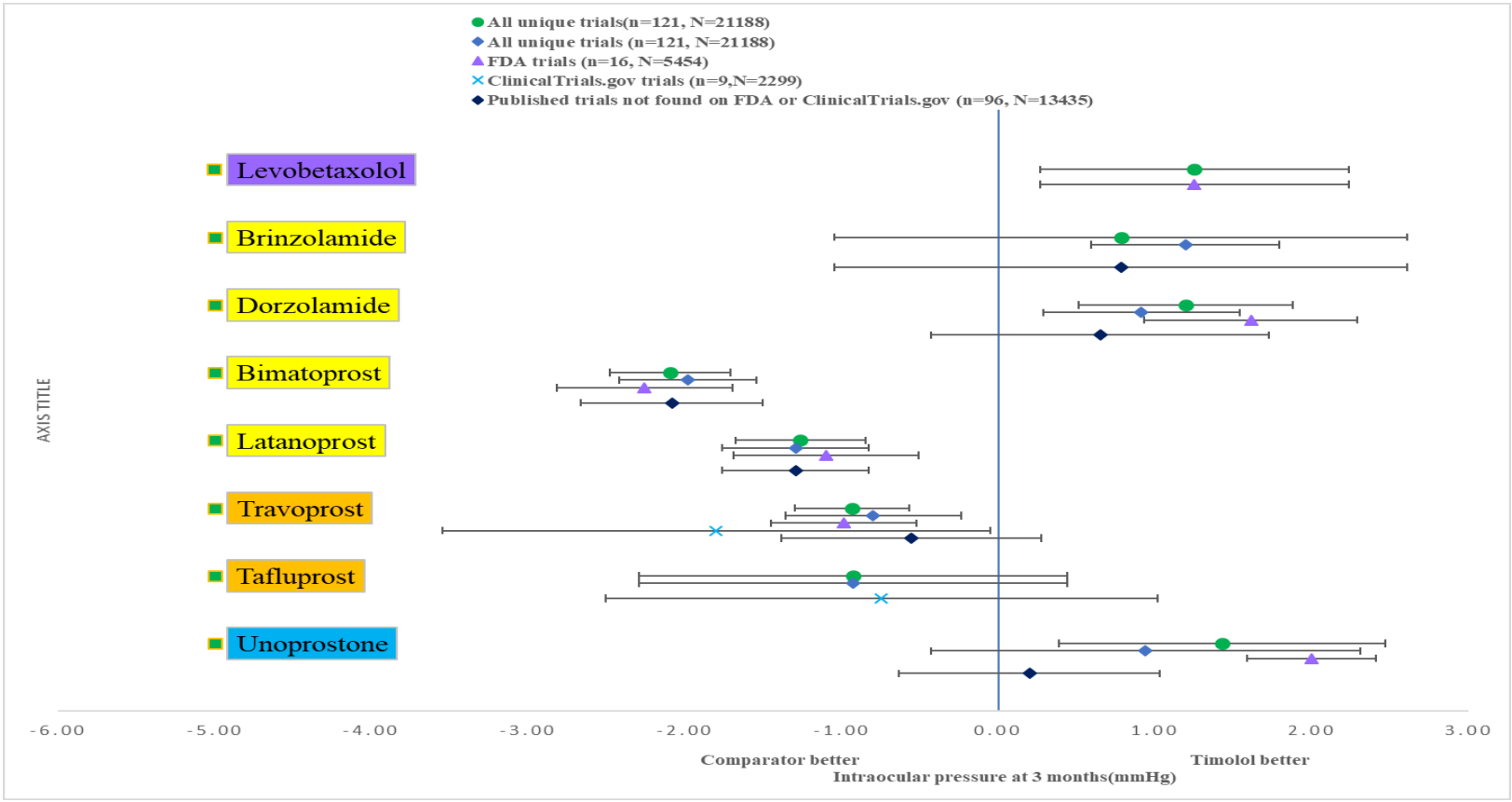
Figure 4.1. Estimated mean difference in intraocular pressure at 3 months derived from pairwise meta-analyses (relative to placebo)



Legend:
Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Figure 4.2. Estimated mean difference in intraocular pressure at 3 months derived from pairwise meta-analyses (relative to timolol)



Notes:
Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Figure 5.1. Network graph (all unique trials)

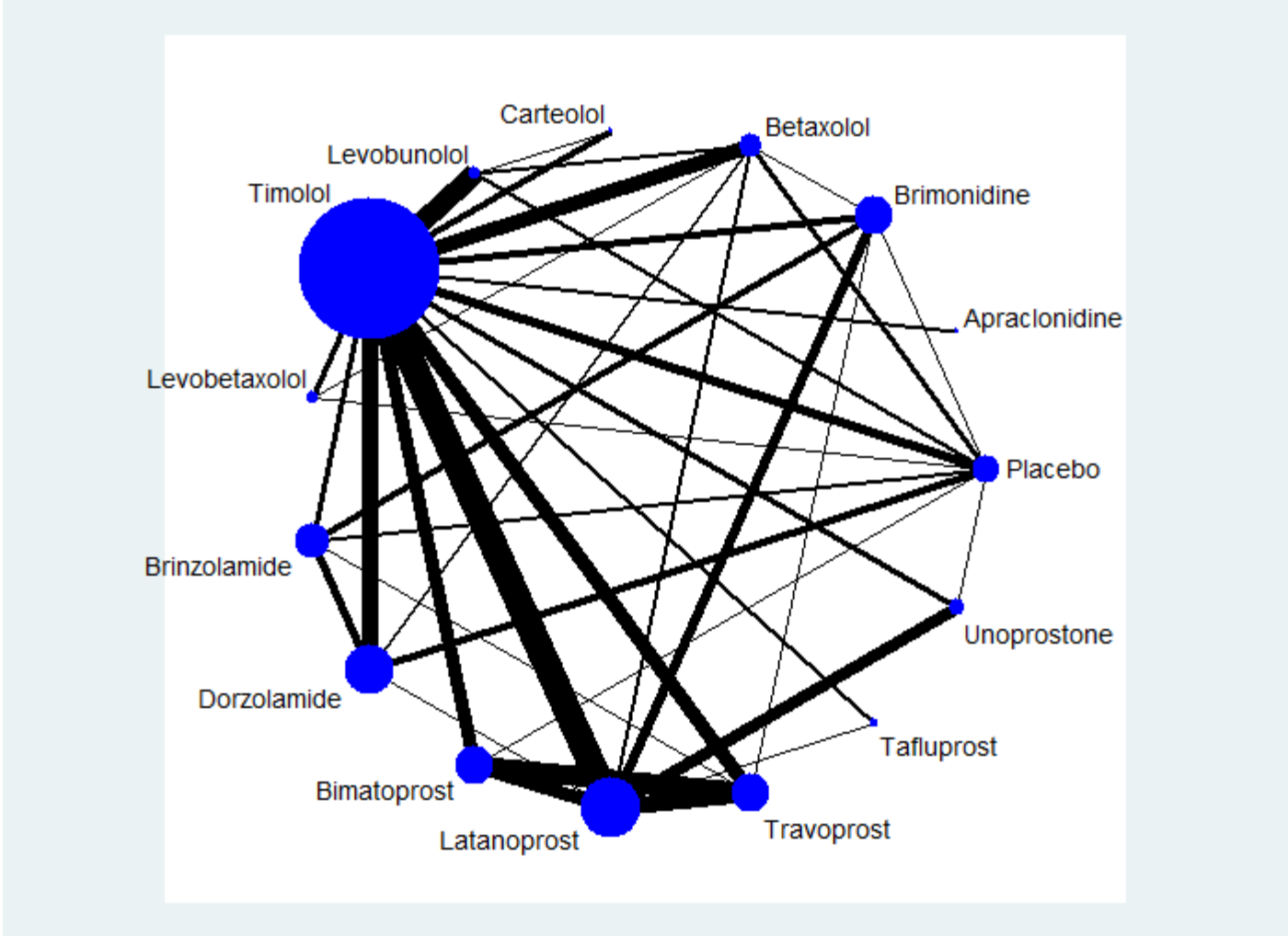


Figure 5.2. Network graph (published trials)

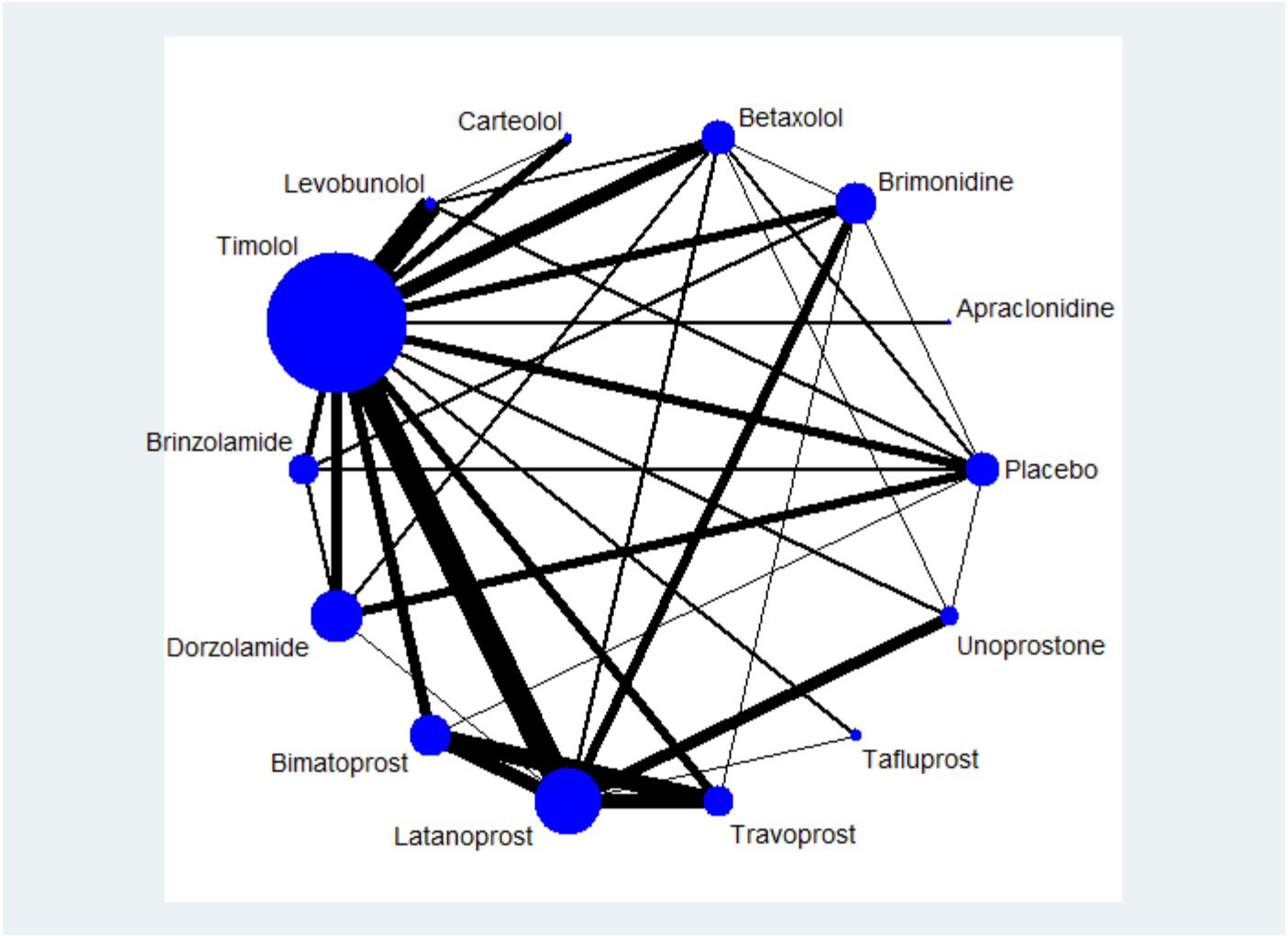


Figure 5.3. Network graph (FDA trials)

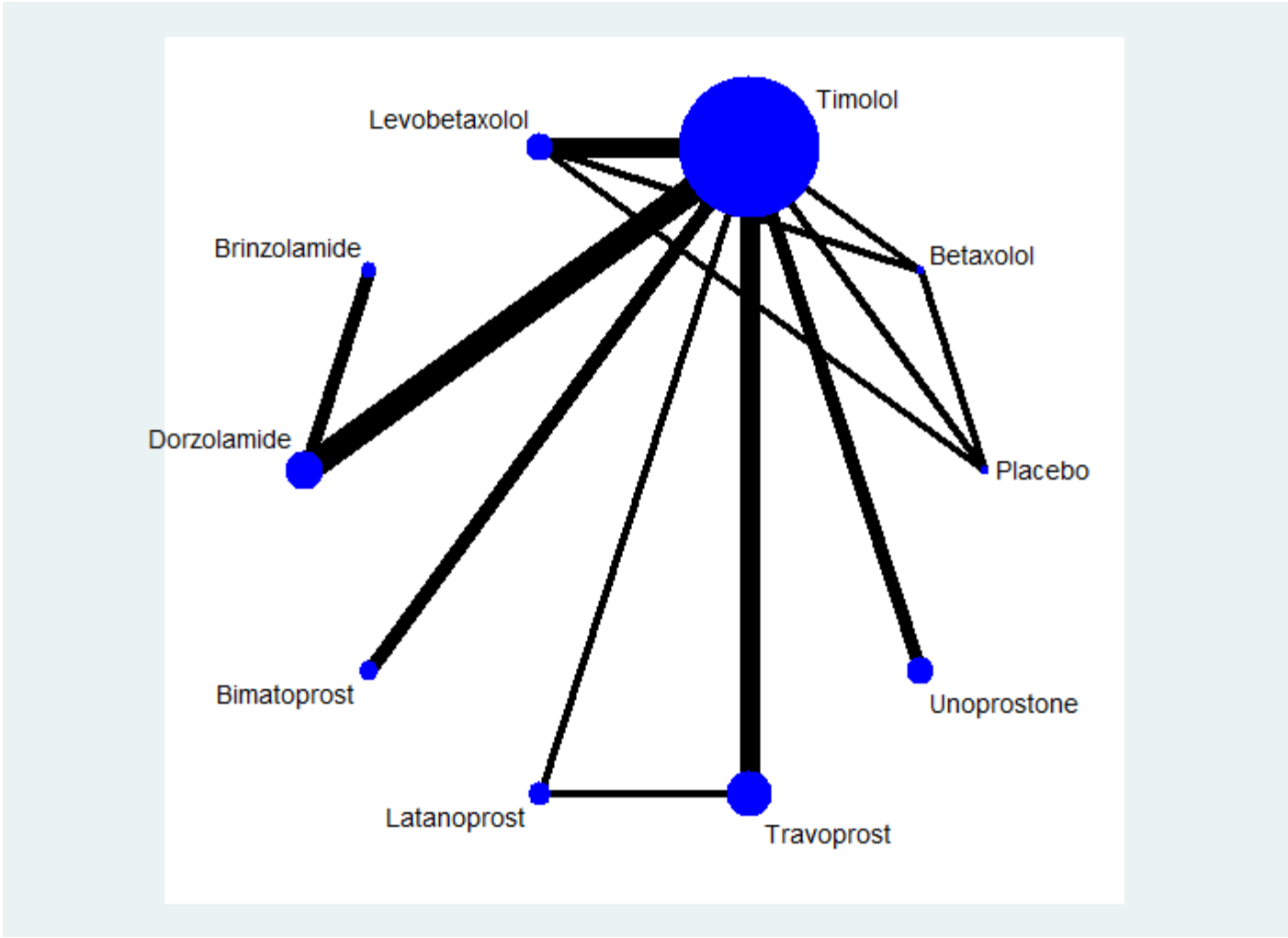


Figure 5.4. Network graph (ClinicalTrials.gov trials)

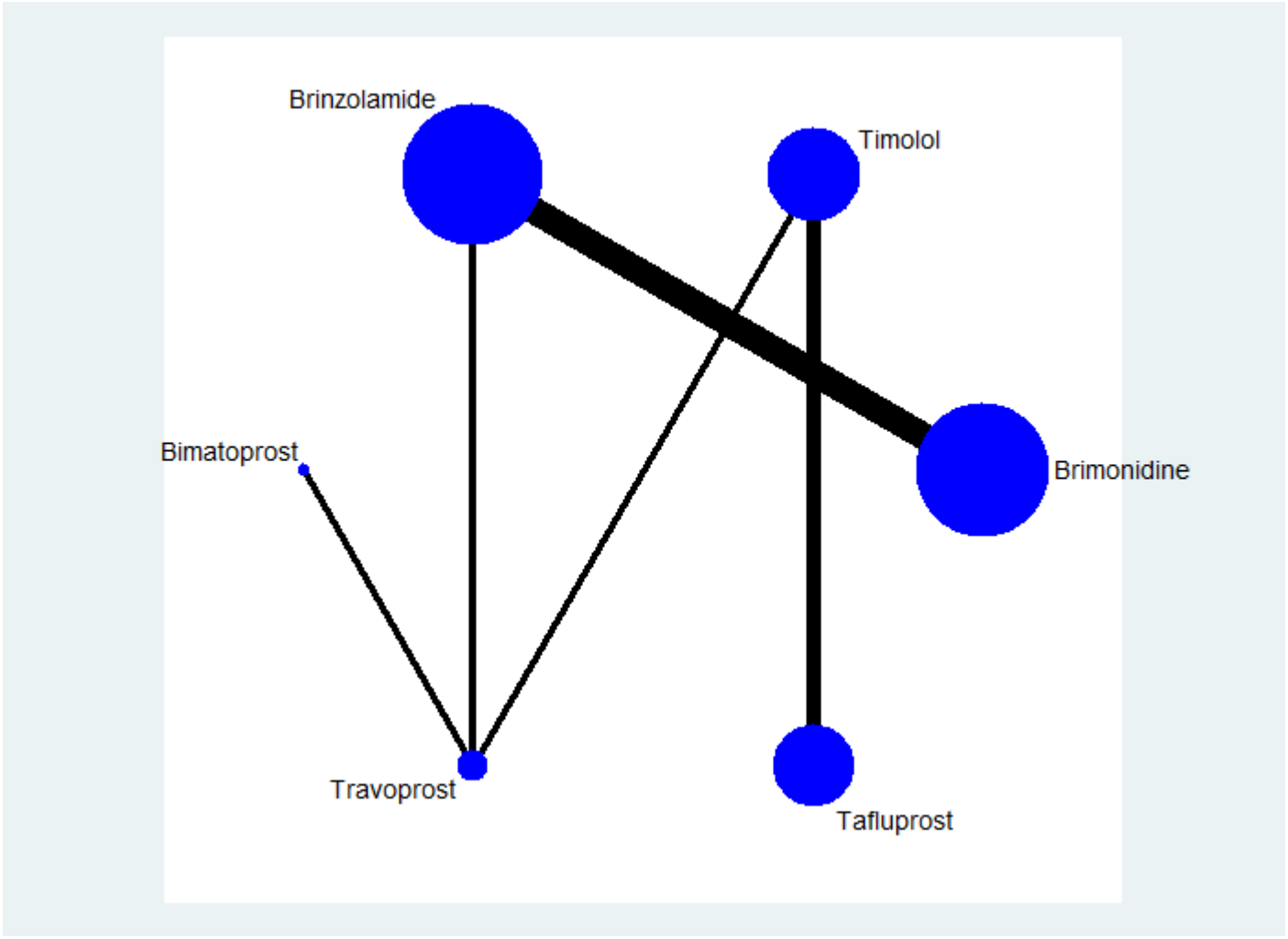
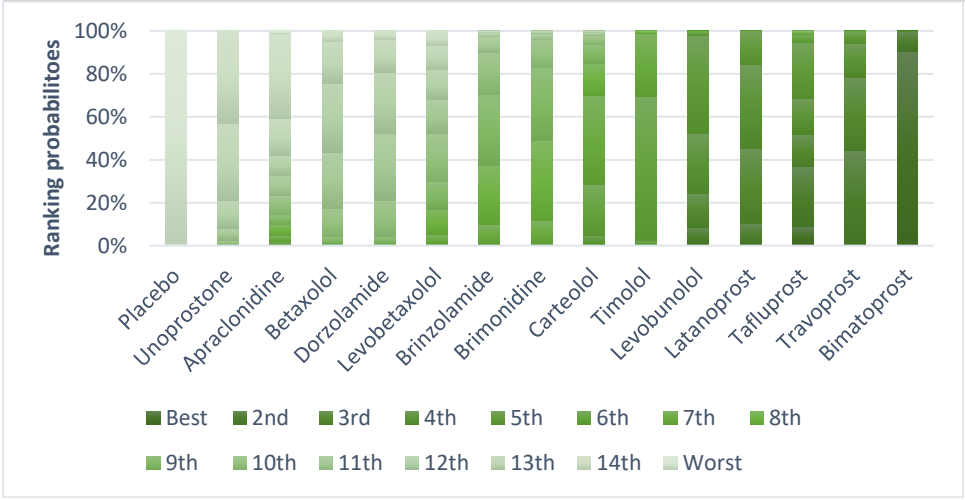


Figure 6.1. Ranking probabilities (all unique trials)

Rank	Placebo	Unoprostone	Apraclonidine	Betaxolol	Dorzolamide	Levobetaxolol	Brinzolamide	Brimonidine	Carteolol	Timolol	Levobunolol	Latanoprost	Tafluprost	Travoprost	Bimatoprost
Best	0	0	0	0	0	0	0	0	0	0	0.3	0	8.9	0.3	90.5
2nd	0	0	0	0	0	0	0	0	0.1	0	8.2	10.2	28	44	9.4
3rd	0	0	0	0	0	0	0	0	0	0	16	35	14.8	34	0.1
4th	0	0	0	0	0	0	0	0	0.5	0	27.9	39	16.6	15.9	0
5th	0	0	0.4	0	0	0	0.1	0	4.3	2.3	45.7	15.5	26	5.6	0
6th	0	0	1.5	0	0	0.9	0.4	0.3	23.6	67.1	1.8	0.2	4	0.1	0
7th	0	0	2.8	0.1	0.1	4.2	9.3	11.4	41.5	29.5	0.1	0	1.2	0	0
8th	0	0.1	5.3	1	0.9	11.9	27.4	37.4	14.7	1.1	0	0	0.3	0	0
9th	0	0.4	4.6	3	3.3	12.8	33.1	33.6	9	0	0	0	0.1	0	0
10th	0	2.1	8.6	13	16.9	22.6	19.7	13	4.1	0	0	0	0	0	0
11th	0	5.6	9.5	26.2	30.8	15.9	7.4	3.2	1.4	0	0	0	0	0	0
12th	0	12.6	9.3	32.3	28.7	13.7	1.9	0.9	0.6	0	0	0	0	0	0
13th	0	36.3	17	19.3	15.3	11.2	0.6	0.1	0.1	0	0	0	0	0	0
14th	1.1	42.9	39.9	5.1	4	6.8	0.1	0	0	0	0	0	0	0	0
Worst	98.9	0	1.1	0	0	0	0	0	0	0	0	0	0	0	0

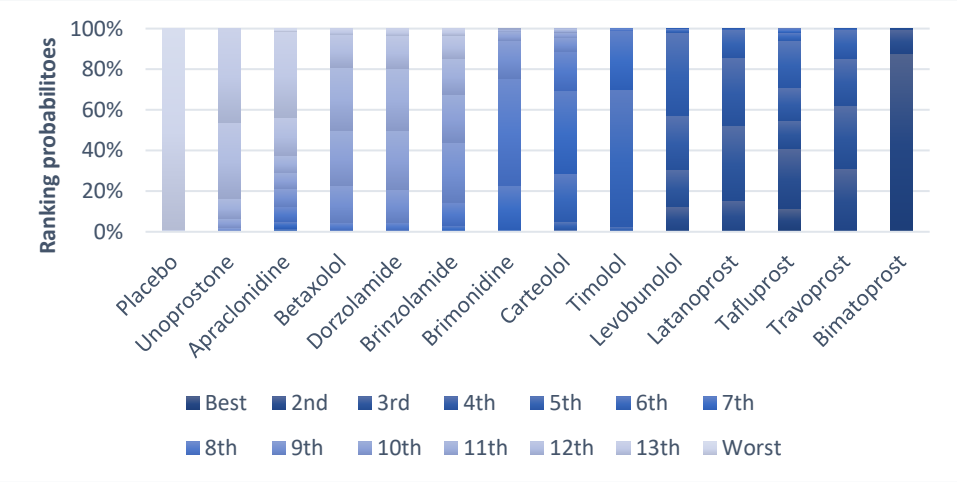


Legend:
Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Figure 6.2. Ranking probabilities (published trials)

Rank	Placebo	Unoprostone	Apraclonidine	Betaxolol	Dorzolamide	Brinzolamide	Brimonidine	Carteolol	Timolol	Levobunolol	Latanoprost	Tafluprost	Travoprost	Bimatoprost
Best	0	0	0	0	0	0	0	0	0	0.6	0	11.3	0.4	87.7
2nd	0	0	0	0	0	0	0	0.1	0	11.6	15.6	29.9	30.8	12.1
3rd	0	0	0	0	0	0	0	0.3	0	18.3	36.6	13.8	30.7	0.2
4th	0	0	0	0	0	0	0	0.6	0	26.5	33.5	15.8	23.5	0
5th	0	0	0.3	0	0	0	0.1	4.1	2.8	41.2	14.1	23.3	14.2	0
6th	0	0	1.5	0	0	0.2	1.2	23.5	67.2	1.7	0.3	4.1	0.3	0
7th	0	0	3.1	0.6	0.6	3	21.3	40.8	29	0.1	0	1.5	0	0
8th	0	0.3	7.3	3.9	4.1	11.2	52.9	19.2	1	0	0	0.2	0	0
9th	0	1.7	8.9	18.1	15.9	29.7	18.7	6.8	0	0	0	0.1	0	0
10th	0	4.7	7.9	27.4	29	23.6	4.4	2.9	0	0	0	0	0	0
11th	0	9.8	8.7	31	30.6	17.4	1.3	1.2	0	0	0	0	0	0
12th	0	37.1	18.6	15.9	16.1	11.6	0.2	0.5	0	0	0	0	0	0
13th	1.3	46.3	42.4	3.1	3.6	3.3	0	0	0	0	0	0	0	0
Worst	98.7	0	1.3	0	0	0	0	0	0	0	0	0	0	0

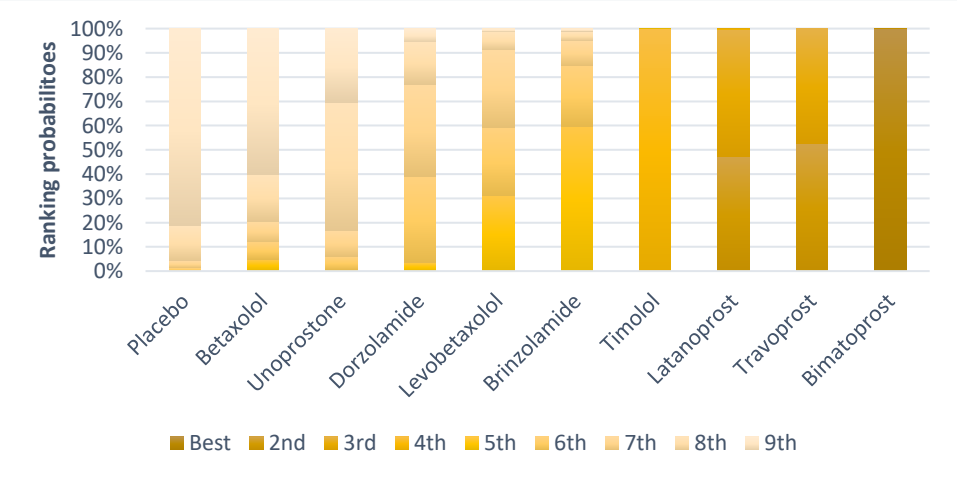


Legend:
Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Figure 6.3. Ranking probabilities (FDA trials)

Rank	Placebo	Betaxolol	Unoprostone	Dorzolamide	Levobetaxolol	Brinzolamide	Timolol	Latanoprost	Travoprost	Bimatoprost
Best	0	0	0	0	0	0	0	0.1	0	99.9
2nd	0	0	0	0	0	0	0	47.2	52.7	0.1
3rd	0	0	0	0	0	0	0.2	52.5	47.3	0
4th	0	0	0	0	0	0.1	99.7	0.2	0	0
5th	0	4.7	0.7	3.7	31.1	59.7	0.1	0	0	0
6th	0.1	6.7	5.1	35.1	28	25	0	0	0	0
7th	0.2	8.2	10.9	38.1	32.2	10.4	0	0	0	0
8th	1	18.4	51.9	17.3	7.6	3.8	0	0	0	0
9th	5.6	56.9	29.9	5.5	1.1	1	0	0	0	0
Worst	93.1	5	1.5	0.3	0	0	0	0	0	0

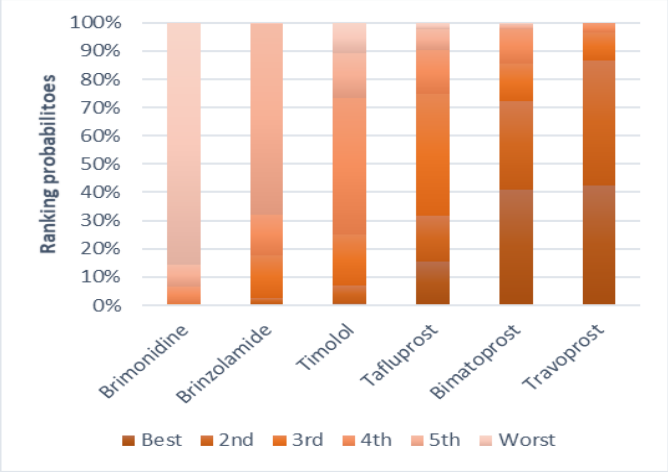


Legend:
Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Figure 6.4. Ranking probabilities (ClinicalTrials.gov trials)

Rank	Brimonidine	Brinzolamide	Timolol	Tafluprost	Bimatoprost	Travoprost
Best	0	0.3	0.7	15.6	41	42.3
2nd	0.1	2.1	6.3	16.1	31.3	44.1
3rd	0.5	15.2	18.1	43	13	10.2
4th	6.1	14.3	48.3	15.7	12.3	3.3
5th	7.7	67.5	16	7.3	1.6	0
Worst	85.6	0.6	10.7	2.3	0.7	0

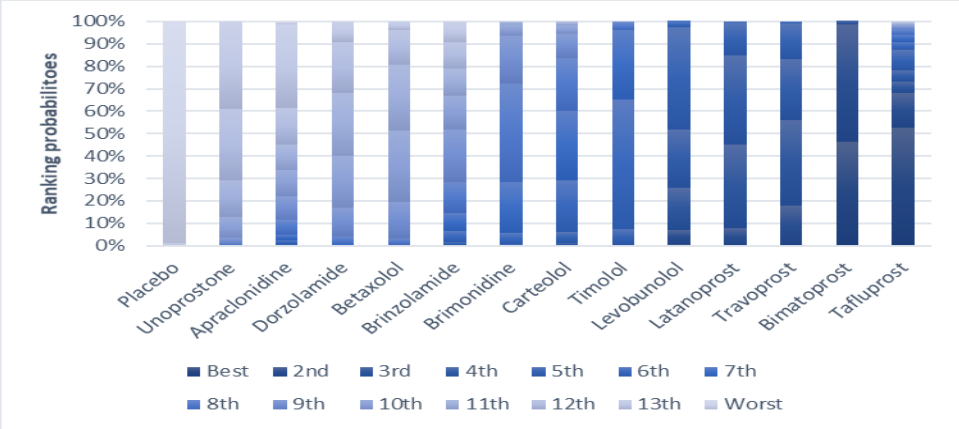


Legend:
Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Figure 6.5. Ranking probabilities (published trials not found on FDA or ClinicalTrials.gov)

Rank	Placebo	Unoprostone	Apraclonidine	Dorzolamide	Betaxolol	Brinzolamide	Brimonidine	Carteolol	Timolol	Levobunolol	Latanoprost	Travoprost	Bimatoprost	Tafluprost
Best	0	0	0	0	0	0	0	0	0	0.5	0	0.3	46.2	52.9
2nd	0	0	0	0	0	0	0	0.1	0	6.4	7.8	17.7	52.7	15.4
3rd	0	0	0	0	0	0.1	0	0.3	0	18.9	37.1	37.9	1	4.8
4th	0	0	0.1	0	0	0.3	0	0.8	0.1	26.1	39.8	27.4	0.1	5.3
5th	0	0	0.5	0	0	1.2	0.5	5.1	7.1	45.4	14.9	15.9	0	9.3
6th	0	0	1.7	0.1	0	5.1	5.2	22.9	58	2.4	0.4	0.7	0	3.4
7th	0	0.1	2.7	0.7	0.3	7.8	22.8	31.1	31.1	0.2	0	0	0	3.2
8th	0	0.5	6.5	3.2	2.8	14	43.9	23.3	3.4	0	0	0	0	2.3
9th	0	3.2	10.4	12.8	16.6	23.1	21.4	11	0.3	0	0	0	0	1.3
10th	0	9.1	12	23.1	31.6	15.1	5	3.6	0	0	0	0	0	0.5
11th	0	16.2	11	28.2	29.4	12.3	0.9	1.2	0	0	0	0	0	0.8
12th	0	32.1	16.6	22.6	15.4	11.9	0.3	0.6	0	0	0	0	0	0.6
13th	1.1	38.9	37.3	9.2	3.9	9.1	0	0	0	0	0	0	0	0.4
Worst	98.9	0	1.1	0	0	0	0	0	0	0	0	0	0	0



Legend:
Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Figure 7.1. Cumulative ranking probabilities (all unique trials)

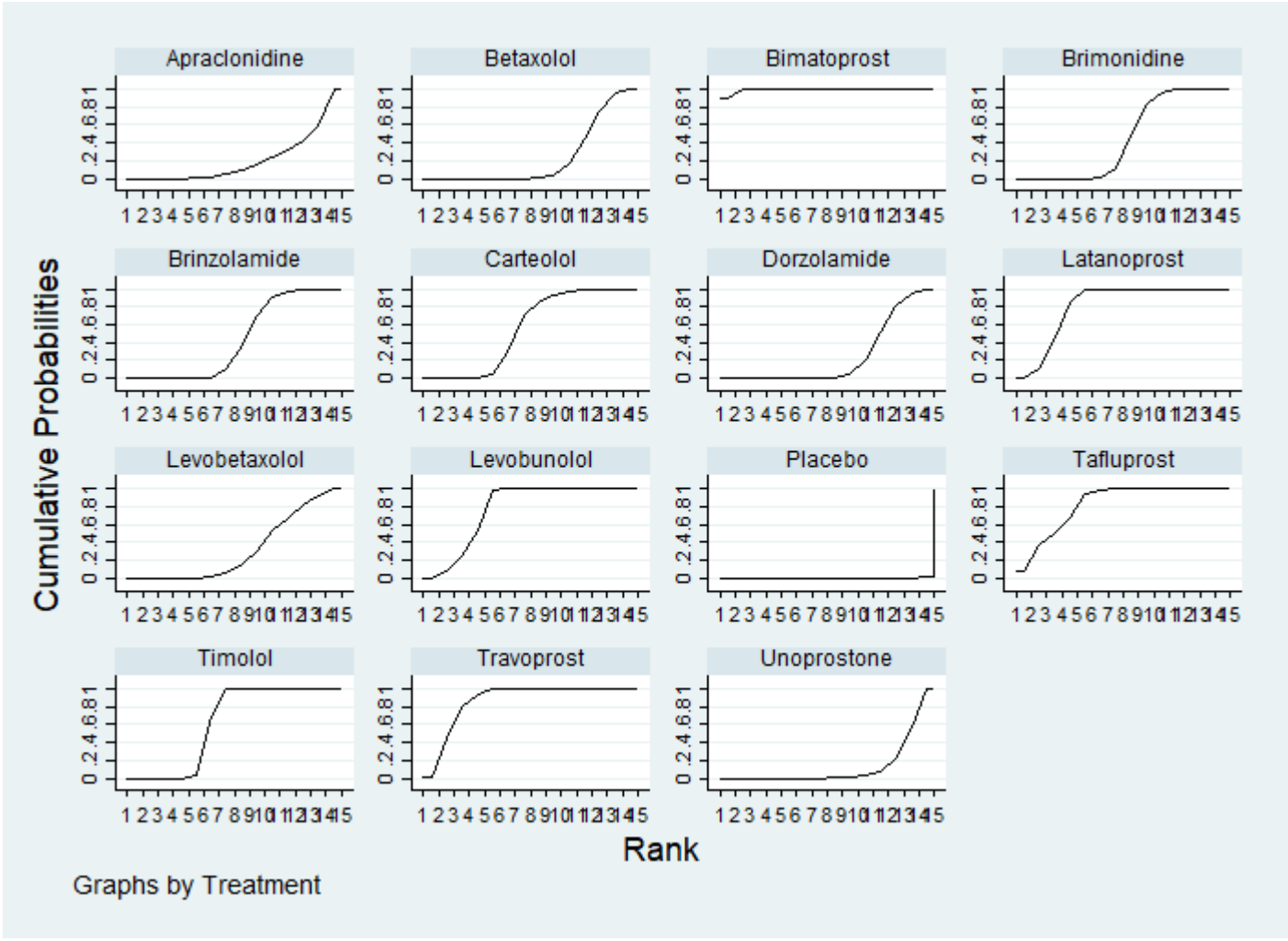


Figure 7.2. Cumulative ranking probabilities (published trials)

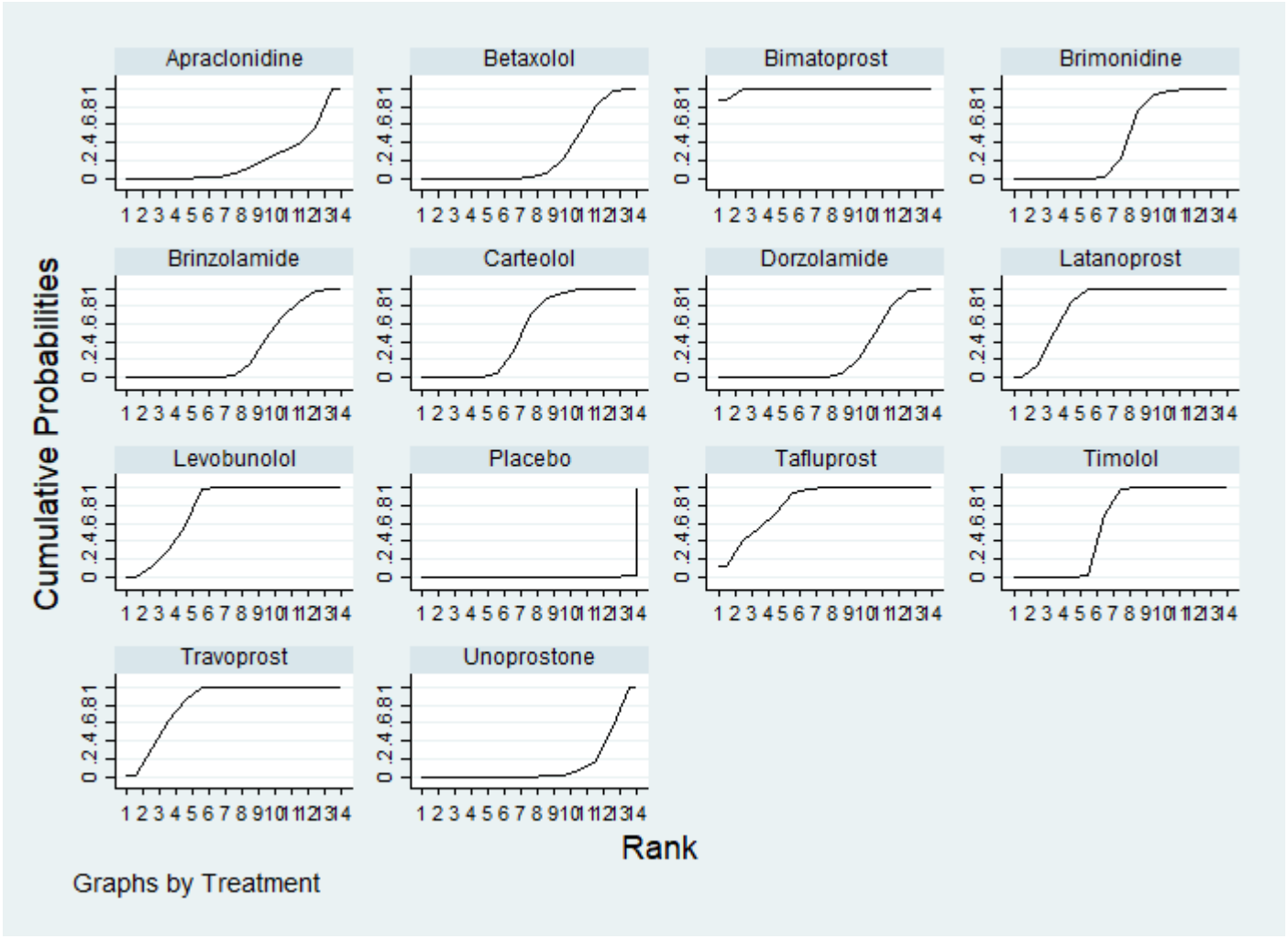


Figure 7.3. Cumulative ranking probabilities (FDA trials)

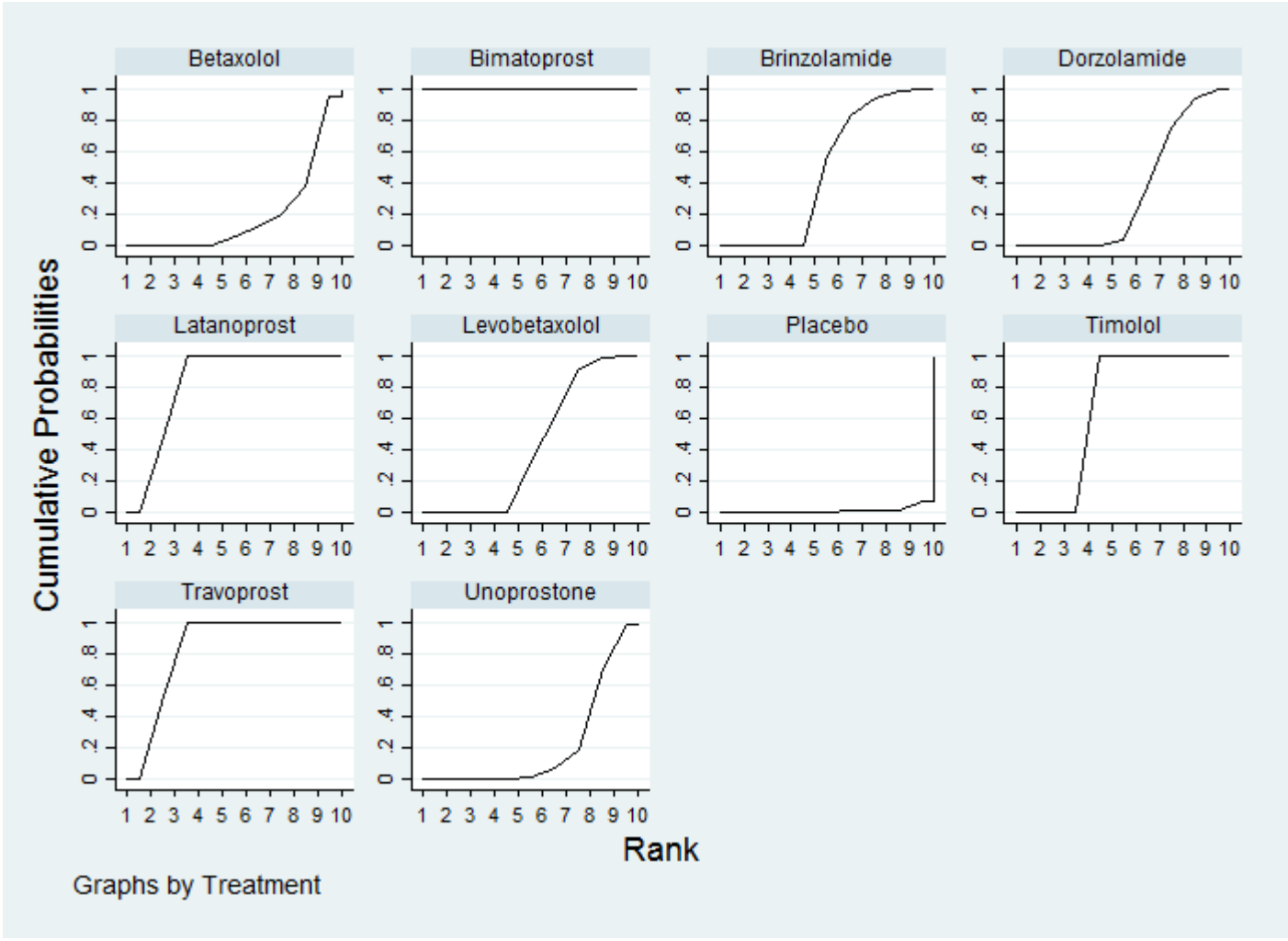


Figure 7.4. Cumulative ranking probabilities (ClinicalTrials.gov trials)

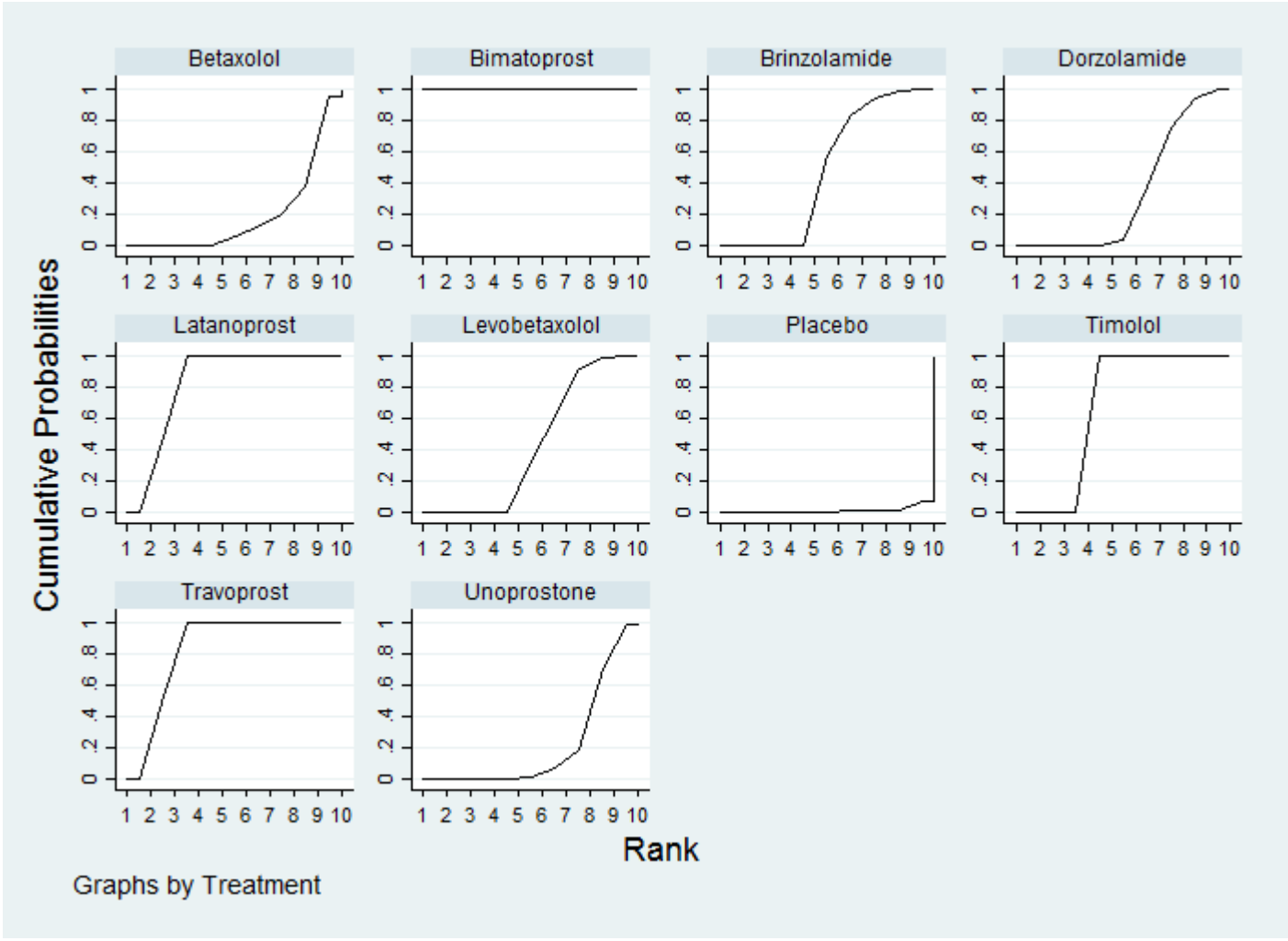


Figure 7.5. Cumulative ranking probabilities (published trials not found on FDA or ClinicalTrials.gov)

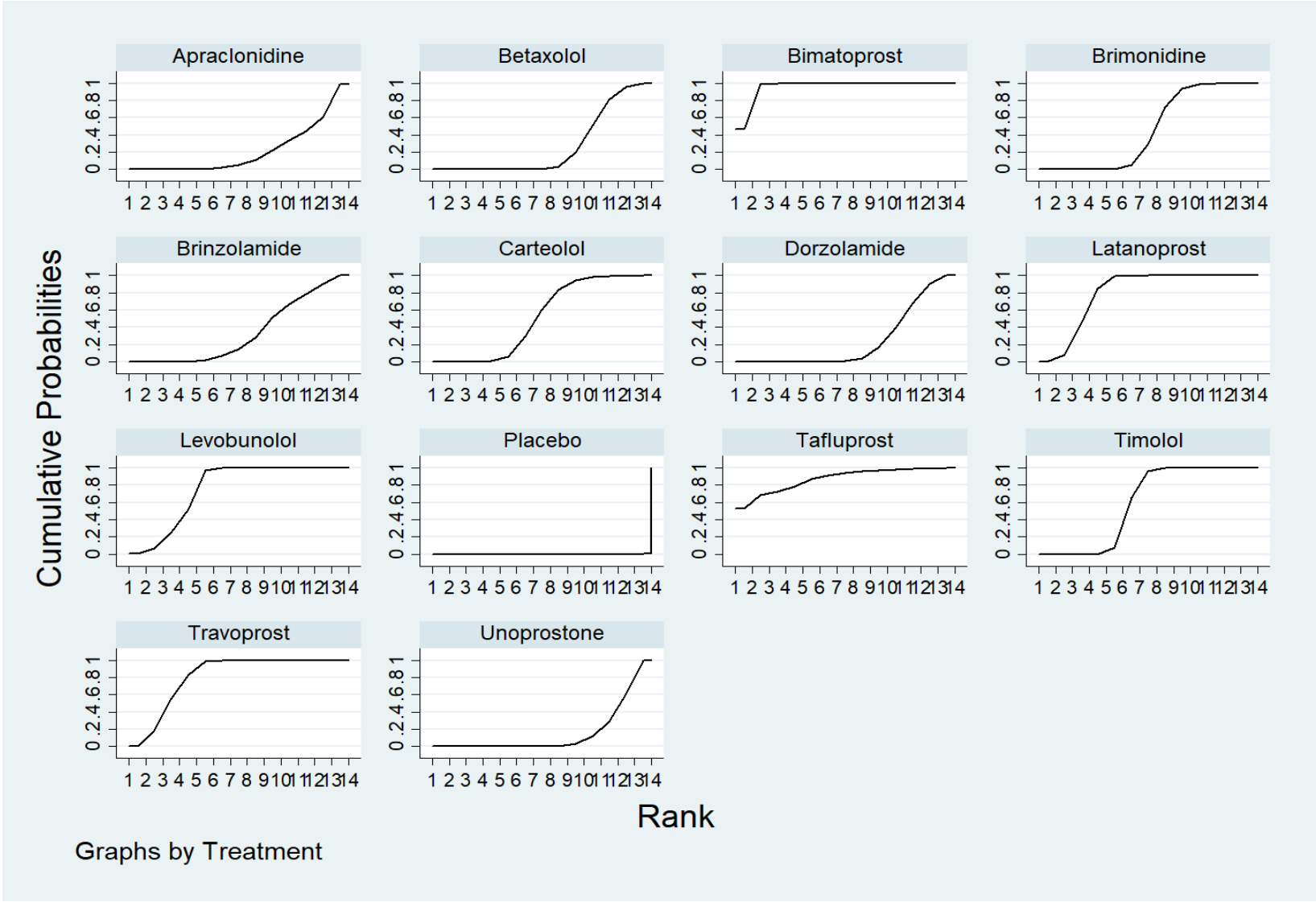
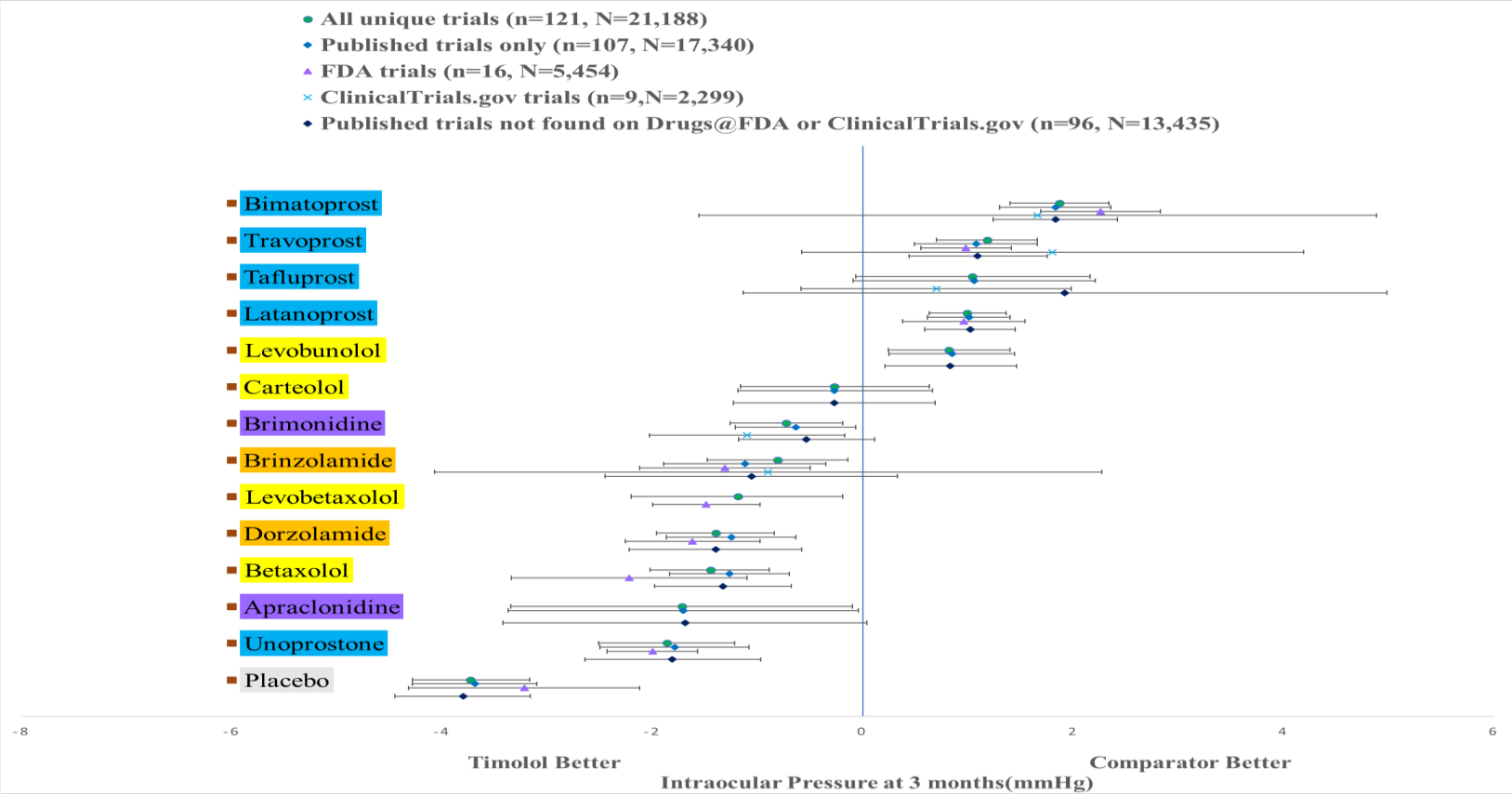


Figure 8. Estimated mean difference in intraocular pressure at 3 months derived from network meta-analyses (relative to timolol)



Legend:
Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

9 Appendices

Appendix 1. Search strategies

ClinicalTrials.gov*
Glaucoma AND (Bimatoprost OR Xalatan OR Travoprost OR Tafluprost OR Unoprostone OR Dorzolamide OR Cosopt OR Brinzolamide OR Timolol OR Levobunolol OR Carteolol OR Betaxolol OR Brimonidine OR Alphagan OR Apraclonidine OR Dipivefrin OR Pilocarpine)

Glaucoma AND (Levobetaxolol OR Echothiophate OR Demecarium OR Metipranolol)

*Two separate strategies due to space limitations in ClinicalTrials.gov search

Appendix 2. Reference to trial reports identified from bibliographic databases

1. Radius RL. Use of betaxolol in the reduction of elevated intraocular pressure. Arch Ophthalmol 1983;101:898-900.
2. Berry DP, Jr., Van Buskirk EM, Shields MB. Betaxolol and timolol. A comparison of efficacy and side effects. Arch Ophthalmol 1984;102:42-5.
3. Bensinger RE, Keates EU, Gofman JD, Novack GD, Duzman E. Levobunolol. A three-month efficacy study in the treatment of glaucoma and ocular hypertension. Arch Ophthalmol 1985;103:375-8.
4. Berson FG, Cohen HB, Foerster RJ, Lass JH, Novack GD, Duzman E. Levobunolol compared with timolol for the long-term control of elevated intraocular pressure. Arch Ophthalmol 1985;103:379-82.
5. Cinotti A, Cinotti D, Grant W, et al. Levobunolol vs timolol for open-angle glaucoma and ocular hypertension. Am J Ophthalmol 1985;99:11-7.
6. Ober M, Scharrer A, David R, et al. Long-term ocular hypotensive effect of levobunolol: results of a one-year study. Br J Ophthalmol 1985;69:593-9.
7. Stryz JR, Merte HJ. Pressure lowering effect and side effects of 0.5% and 1.0% levobunolol eyedrops, compared with 0.5% timolol eyedrops in patients with open-angle glaucoma. Klin Monbl Augenheilkd 1985;187:537-44.
8. Stewart RH, Kimbrough RL, Ward RL. Betaxolol vs timolol. A six-month double-blind comparison. Arch Ophthalmol 1986;104:46-8.
9. Boozman FW, 3rd, Carriker R, Foerster R, Allen RC, Novack GD, Batoosingh AL. Long-term evaluation of 0.25% levobunolol and timolol for therapy for elevated intraocular pressure. Arch Ophthalmol 1988;106:614-8.
10. Feghali JG, Kaufman PL, Radius RL, Mandell AI. A comparison of betaxolol and timolol in open angle glaucoma and ocular hypertension. Acta Ophthalmol (Copenh) 1988;66:180-6.
11. Freyler H, Novack GD, Menapace R, Skorpik C, Mordaunt J, Batoosingh AL. Comparison of the effectiveness and safety of levobunolol and timolol in ocular hypertension and chronic open-angle glaucoma. Klin Monbl Augenheilkd 1988;193:257-60.
12. Long DA, Johns GE, Mullen RS, et al. Levobunolol and betaxolol. A double-masked controlled comparison of efficacy and safety in patients with elevated intraocular pressure. Ophthalmology 1988;95:735-41.
13. Seamone C, LeBlanc R, Saheb N, Novack G. Efficacy of twice-daily levobunolol in the treatment of elevated intraocular pressure. Can J Ophthalmol 1988;23:168-70.
14. Epstein DL, Krug JH, Jr., Hertzmark E, Remis LL, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. Ophthalmology 1989;96:1460-7.
15. Kass MA, Gordon MO, Hoff MR, et al. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals. A randomized, double-masked, long-term clinical trial. Arch Ophthalmol 1989;107:1590-8.
16. Yoshiaki K, Ikuo A, Makoto A. Clinical evaluation of betaxolol hydrochloride in the treatment of primary open angle glaucoma and ocular hypertension. Multi-center

double-masked study in comparison with timolol. Rinsho Hyoka (Clinical Evaluation) 1989;17:243-74.
17. Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. Ophthalmology 1991;98:301-7.
18. Silverstone D, Zimmerman T, Choplin N, et al. Evaluation of once-daily levobunolol 0.25% and timolol 0.25% therapy for increased intraocular pressure. Am J Ophthalmol 1991;112:56-60.
19. Beehler CC, Stewart WC, Macdonald DK, et al. A comparison of the ocular hypotensive efficacy of twice-daily 0.25% levobunolol to 0.5% timolol in patients previously treated with 0.5% timolol. J Glaucoma 1992;1:237-42.
20. Flammer J, Kitazawa Y, Bonomi L, et al. Influence of carteolol and timolol on IOP an visual fields in glaucoma: a multi-center, double-masked, prospective study. Eur J Ophthalmol 1992;2:169-74.
21. Azuma I, Masuda K, Kitazawa Y, Takase M, Yamamura H. Double-masked comparative study of UF-021 and timolol ophthalmic solutions in patients with primary open-angle glaucoma or ocular hypertension. Jpn J Ophthalmol 1993;37:514-25.
22. Nagasubramanian S, Hitchings RA, Demailly P, et al. Comparison of apraclonidine and timolol in chronic open-angle glaucoma. A three-month study. Ophthalmology 1993;100:1318-23.
23. Wilkerson M, Cyrlin M, Lippa EA, et al. Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. Arch Ophthalmol 1993;111:1343-50.
24. Behrens-Baumann W, Kimmich F, Walt JG, Lue J. A comparison of the ocular hypotensive efficacy and systemic safety of 0.5% levobunolol and 2% carteolol. Ophthalmologica 1994;208:32-6.
25. Kitazawa Y. Phase III comparative study of MK-507 ophthalmic solution in primary open-angle glaucoma and ocular hypertension. Folia Ophthalmol Jpn 1994;45:1023-33.
26. Ravalico G, Salvetat L, Toffoli G, Pastori G, Croce M, Battaglia P. Ocular hypertension: A follow-up study in treated and untreated patients. New Trends Ophthalmol 1994;9:97-101.
27. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian Latanoprost Study Group. Ophthalmology 1995;102:1743-52.
28. Schwartz B, Lavin P, Takamoto T, Araujo DF, Smits G. Decrease of optic disc cupping and pallor of ocular hypertensives with timolol therapy. Acta Ophthalmol Scand Suppl 1995:5-21.
29. Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. Arch Ophthalmol 1995;113:1009-16.
30. Fristrom B. A 6-month, randomized, double-masked comparison of latanoprost with timolol in patients with open angle glaucoma or ocular hypertension. Acta Ophthalmol Scand 1996;74:140-4.
31. Mishima HK, Masuda K, Kitazawa Y, Azuma I, Araie M. A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week study. Arch Ophthalmol 1996;114:929-32.

32. Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. Surv Ophthalmol 1996;41 Suppl 1:S27-37.
33. Serle JB. A comparison of the safety and efficacy of twice daily brimonidine 0.2% versus betaxolol 0.25% in subjects with elevated intraocular pressure. The Brimonidine Study Group III. Surv Ophthalmol 1996;41 Suppl 1:S39-47.
34. Stewart WC, Laibovitz R, Horwitz B, Stewart RH, Ritch R, Kottler M. A 90-day study of the efficacy and side effects of 0.25% and 0.5% apraclonidine vs 0.5% timolol. Apraclonidine Primary Therapy Study Group. Arch Ophthalmol 1996;114:938-42.
35. Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. Ophthalmology 1996;103:126-37.
36. Yamamoto T, Kitazawa Y, Noma A, et al. The effects of the beta-adrenergic-blocking agents, timolol and carteolol, on plasma lipids and lipoproteins in Japanese glaucoma patients. J Glaucoma 1996;5:252-7.
37. Kitazawa Y, Azuma I, Shirato S, et al. Phase III Clinical Study of AG-901 Ophthalmic Solution on Primary Open-Angle Glaucoma and Ocular Hypertension: A Multicenter, Double-Blind Comparison with 0.5% Timolol Maleate. Journal of Clinical Therapeutics and Medicines 1997;13:2975-91.
38. Stewart WC, Cohen JS, Netland PA, Weiss H, Nussbaum LL. Efficacy of carteolol hydrochloride 1% vs timolol maleate 0.5% in patients with increased intraocular pressure. Nocturnal Investigation of Glaucoma Hemodynamics Trial Study Group. Am J Ophthalmol 1997;124:498-505.
39. Boyle JE, Ghosh K, Gieser DK, Adamsons IA. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide. Dorzolamide-Timolol Study Group. Ophthalmology 1998;105:1945-51.
40. Clineschmidt CM, Williams RD, Snyder E, Adamsons IA. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Dorzolamide-Timolol Combination Study Group. Ophthalmology 1998;105:1952-9.
41. Diestelhorst M, Almegard B. Comparison of two fixed combinations of latanoprost and timolol in open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol 1998;236:577-81.
42. LeBlanc RP. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. Brimonidine Study Group 2. Ophthalmology 1998;105:1960-7.
43. Rusk C, Sharpe E, Laurence J, Polis A, Adamsons I. Comparison of the efficacy and safety of 2% dorzolamide and 0.5% betaxolol in the treatment of elevated intraocular pressure. Dorzolamide Comparison Study Group. Clin Ther 1998;20:454-66.
44. Silver LH. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Brinzolamide Primary Therapy Study Group. Am J Ophthalmol 1998;126:400-8.
45. Bojic L, Bagatin J, Ivanisevic M, Hozo I, Racic G, Karelovic D. Influence of betaxolol and timolol on the venous tone in glaucoma patients. Int Ophthalmol 1999;23:149-53.

46. Stewart WC, Dubiner HB, Mundorf TK, et al. Effects of carteolol and timolol on plasma lipid profiles in older women with ocular hypertension or primary open-angle glaucoma. Am J Ophthalmol 1999;127:142-7.
47. Toris CB, Camras CB, Yablonski ME. Acute versus chronic effects of brimonidine on aqueous humor dynamics in ocular hypertensive patients. Am J Ophthalmol 1999;128:8-14.
48. Alm A, Widengard I. Latanoprost: experience of 2-year treatment in Scandinavia. Acta Ophthalmol Scand 2000;78:71-6.
49. O'Donoghue EP. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a 3 month, randomised study. Ireland Latanoprost Study Group. Br J Ophthalmol 2000;84:579-82.
50. Sall K. The efficacy and safety of brinzolamide 1% ophthalmic suspension (Azopt) as a primary therapy in patients with open-angle glaucoma or ocular hypertension. Brinzolamide Primary Therapy Study Group. Surv Ophthalmol 2000;44 Suppl 2:S155-62.
51. Brandt JD, VanDenburgh AM, Chen K, Whitcup SM, Bimatoprost Study G. Comparison of once- or twice-daily bimatoprost with twice-daily timolol in patients with elevated IOP : a 3-month clinical trial. Ophthalmology 2001;108:1023-31; discussion 32.
52. Bron AM, Denis P, Nordmann JP, Rouland JF, Sellem E, Johansson M. Additive IOP-reducing effect of latanoprost in patients insufficiently controlled on timolol. Acta ophthalmologica Scandinavica 2001;79:289-93.
53. DuBiner HB, Mroz M, Shapiro AM, Dirks MS, Brimonidine vs. Latanoprost Study G. A comparison of the efficacy and tolerability of brimonidine and latanoprost in adults with open-angle glaucoma or ocular hypertension: a three-month, multicenter, randomized, double-masked, parallel-group trial. Clin Ther 2001;23:1969-83.
54. Goldberg I, Cunha-Vaz J, Jakobsen JE, et al. Comparison of topical travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension. J Glaucoma 2001;10:414-22.
55. Kobayashi H, Kobayashi K, Okinami S. A comparison of intraocular pressure-lowering effect of prostaglandin F2 -alpha analogues, latanoprost, and unoprostone isopropyl. J Glaucoma 2001;10:487-92.
56. Netland PA, Landry T, Sullivan EK, et al. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001;132:472-84.
57. Susanna R, Jr., Giampani J, Jr., Borges AS, Vessani RM, Jordao ML. A double-masked, randomized clinical trial comparing latanoprost with unoprostone in patients with open-angle glaucoma or ocular hypertension. Ophthalmology 2001;108:259-63.
58. Aung T, Chew PT, Oen FT, et al. Additive effect of unoprostone and latanoprost in patients with elevated intraocular pressure. Br J Ophthalmol 2002;86:75-9.
59. Bergstrand IC, Heijl A, Harris A. Dorzolamide and ocular blood flow in previously untreated glaucoma patients: a controlled double-masked study. Acta Ophthalmol Scand 2002;80:176-82.
60. Fellman RL, Sullivan EK, Ratliff M, et al. Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated intraocular pressure: a 6-month, masked, multicenter trial. Ophthalmology 2002;109:998-1008.

61. Higginbotham EJ, Feldman R, Stiles M, Dubiner H, Fixed Combination Investigative G. Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. Arch Ophthalmol 2002;120:915-22.
62. Jampel HD, Bacharach J, Sheu WP, et al. Randomized clinical trial of latanoprost and unoprostone in patients with elevated intraocular pressure. Am J Ophthalmol 2002;134:863-71.
63. Kampik A, Arias-Puente A, O'Brart DP, Vuori ML, European Latanoprost Study G. Intraocular pressure-lowering effects of latanoprost and brimonidine therapy in patients with open-angle glaucoma or ocular hypertension: a randomized observer-masked multicenter study. J Glaucoma 2002;11:90-6.
64. Nordmann JP, Mertz B, Yannoulis NC, et al. A double-masked randomized comparison of the efficacy and safety of unoprostone with timolol and betaxolol in patients with primary open-angle glaucoma including pseudoexfoliation glaucoma or ocular hypertension. 6 month data. Am J Ophthalmol 2002;133:1-10.
65. Pfeiffer N, European Latanoprost Fixed Combination Study G. A comparison of the fixed combination of latanoprost and timolol with its individual components. Graefes Arch Clin Exp Ophthalmol 2002;240:893-9.
66. Simmons ST, Earl ML, Alphagan/Xalatan Study G. Three-month comparison of brimonidine and latanoprost as adjunctive therapy in glaucoma and ocular hypertension patients uncontrolled on beta-blockers: tolerance and peak intraocular pressure lowering. Ophthalmology 2002;109:307-14; discussion 14-5.
67. Sponsel WE, Paris G, Trigo Y, Pena M. Comparative effects of latanoprost (Xalatan) and unoprostone (Rescula) in patients with open-angle glaucoma and suspected glaucoma. Am J Ophthalmol 2002;134:552-9.
68. Tsukamoto H, Mishima HK, Kitazawa Y, et al. A comparative clinical study of latanoprost and isopropyl unoprostone in Japanese patients with primary open-angle glaucoma and ocular hypertension. J Glaucoma 2002;11:497-501.
69. Camras CB, Hedman K, Group USLS. Rate of response to latanoprost or timolol in patients with ocular hypertension or glaucoma. J Glaucoma 2003;12:466-9.
70. Cardascia N, Vetrugno M, Trabucco T, Cantatore F, Sborgia C. Effects of travoprost eye drops on intraocular pressure and pulsatile ocular blood flow: a 180-day, randomized, double-masked comparison with latanoprost eye drops in patients with open-angle glaucoma. Curr Ther Res Clin Exp 2003;64:389-400.
71. Inan UU, Ermis SS, Yucel A, Ozturk F. The effects of latanoprost and brimonidine on blood flow velocity of the retrobulbar vessels: a 3-month clinical trial. Acta Ophthalmol Scand 2003;81:155-60.
72. Kamal D, Garway-Heath D, Ruben S, et al. Results of the betaxolol versus placebo treatment trial in ocular hypertension. Graefes Arch Clin Exp Ophthalmol 2003;241:196-203.
73. Parrish RK, Palmberg P, Sheu WP, Group XLTS. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol 2003;135:688-703.
74. Whitcup SM, Cantor LB, VanDenburgh AM, Chen K. A randomised, double masked, multicentre clinical trial comparing bimatoprost and timolol for the treatment of glaucoma and ocular hypertension. Br J Ophthalmol 2003;87:57-62.

75. Erkin EF, Tarhan S, Kayikcioglu OR, Deveci H, Guler C, Goktan C. Effects of betaxolol and latanoprost on ocular blood flow and visual fields in patients with primary open-angle glaucoma. Eur J Ophthalmol 2004;14:211-9.
76. Kobayashi H, Iwakiri R, Kobayashi K, Okinami S. Hypotensive effect of unoprostone as adjunct to latanoprost during multiple drug therapy for glaucoma. Japanese Journal of Clinical Ophthalmology 2004;58:193-7.
77. Vetrugno M, Cardascia N, Cantatore F, Sborgia C. Comparison of the effects of bimatoprost and timolol on intraocular pressure and pulsatile ocular blood flow in patients with primary open-angle glaucoma: A prospective, open-label, randomized, two-arm, parallel-group study. Curr Ther Res Clin Exp 2004;65:444-54.
78. Walters TR, DuBiner HB, Carpenter SP, Khan B, VanDenburgh AM, Bimatoprost Circadian IOPSG. 24-Hour IOP control with once-daily bimatoprost, timolol gel-forming solution, or latanoprost: a 1-month, randomized, comparative clinical trial. Surv Ophthalmol 2004;49 Suppl 1:S26-35.
79. Wang TH, Huang JY, Hung PT, Shieh JW, Chen YF. Ocular hypotensive effect and safety of brinzolamide ophthalmic solution in open angle glaucoma patients. J Formos Med Assoc 2004;103:369-73.
80. Barnebey HS, Orengo-Nania S, Flowers BE, et al. The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. Am J Ophthalmol 2005;140:1-7.
81. Camras CB, Sheu WP, United States Latanoprost-Brimonidine Study G. Latanoprost or brimonidine as treatment for elevated intraocular pressure: multicenter trial in the United States. J Glaucoma 2005;14:161-7.
82. Miglior S, Zeyen T, Pfeiffer N, et al. Results of the European Glaucoma Prevention Study. Ophthalmology 2005;112:366-75.
83. Erkin EF, Celik P, Kayikcioglu O, Deveci HM, Sakar A. Effects of latanoprost and betaxolol on cardiovascular and respiratory status of newly diagnosed glaucoma patients. Ophthalmologica 2006;220:332-7.
84. Sherwood MB, Craven ER, Chou C, et al. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. Arch Ophthalmol 2006;124:1230-8.
85. Koz OG, Ozsoy A, Yarangumeli A, Kose SK, Kural G. Comparison of the effects of travoprost, latanoprost and bimatoprost on ocular circulation: a 6-month clinical trial. Acta Ophthalmol Scand 2007;85:838-43.
86. Martin E, Martinez-de-la-Casa JM, Garcia-Feijoo J, Troyano J, Larrosa JM, Garcia-Sanchez J. A 6-month assessment of bimatoprost 0.03% vs timolol maleate 0.5%: hypotensive efficacy, macular thickness and flare in ocular-hypertensive and glaucoma patients. Eye (Lond) 2007;21:164-8.
87. Alagoz G, Gurel K, Bayer A, Serin D, Celebi S, Kukner S. A comparative study of bimatoprost and travoprost: effect on intraocular pressure and ocular circulation in newly diagnosed glaucoma patients. Ophthalmologica 2008;222:88-95.
88. Brandt JD, Cantor LB, Katz LJ, et al. Bimatoprost/timolol fixed combination: a 3-month double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension. J Glaucoma 2008;17:211-6.

89. Kaback M, Scoper SV, Arzeno G, et al. Intraocular pressure-lowering efficacy of brinzolamide 1%/timolol 0.5% fixed combination compared with brinzolamide 1% and timolol 0.5%. Ophthalmology 2008;115:1728-34, 34 e1-2.
90. Williams RD, Cohen JS, Gross RL, et al. Long-term efficacy and safety of bimatoprost for intraocular pressure lowering in glaucoma and ocular hypertension: year 4. Br J Ophthalmol 2008;92:1387-92.
91. Yildirim N, Sahin A, Gultekin S. The effect of latanoprost, bimatoprost, and travoprost on circadian variation of intraocular pressure in patients with open-angle glaucoma. J Glaucoma 2008;17:36-9.
92. Casson RJ, Liu L, Graham SL, et al. Efficacy and safety of bimatoprost as replacement for latanoprost in patients with glaucoma or ocular hypertension: a uniocular switch study. Journal of glaucoma 2009;18:582-8.
93. Prata TS, Piassi MV, Melo LA, Jr. Changes in visual function after intraocular pressure reduction using antiglaucoma medications. Eye (Lond) 2009;23:1081-5.
94. Sharma R, Kohli K, Kapoor B, Mengi RK, Sadhotra P. The cardio-vascular effects of topical timolol, levobunolol and betaxolol in patients of chronic simple glaucoma. Journal of Clinical and Diagnostic Research 2009;3:1615-20.
95. Zhao WJ. [Comparison of travoprost and timolol in patients with primary open angle glaucoma and ocular hypertension]. International Journal of Ophthalmology 2009;9:1753-4.
96. Birt CM, Buys YM, Ahmed, II, Trope GE. Prostaglandin efficacy and safety study undertaken by race (the PRESSURE study). Journal of glaucoma 2010;19:460-7.
97. Craven ER, Liu CC, Batoosingh A, Schiffman RM, Whitcup SM. A randomized, controlled comparison of macroscopic conjunctival hyperemia in patients treated with bimatoprost 0.01% or vehicle who were previously controlled on latanoprost. Clin Ophthalmol 2010;4:1433-40.
98. Fuchsjager-Mayrl G, Georgopoulos M, Hommer A, et al. Effect of dorzolamide and timolol on ocular pressure: blood flow relationship in patients with primary open-angle glaucoma and ocular hypertension. Invest Ophthalmol Vis Sci 2010;51:1289-96.
99. Higginbotham EJ, Olander KW, Kim EE, Grunden JW, Kwok KK, Tressler CS. Fixed combination of latanoprost and timolol vs individual components for primary open-angle glaucoma or ocular hypertension: a randomized, double-masked study. Archives of ophthalmology 2010;128:165-72.
100. Kammer JA, Katzman B, Ackerman SL, Hollander DA. Efficacy and tolerability of bimatoprost versus travoprost in patients previously on latanoprost: a 3-month, randomised, masked-evaluator, multicentre study. The British journal of ophthalmology 2010;94:74-9.
101. Katz G, Springs CL, Craven ER, Montecchi-Palmer M. Ocular surface disease in patients with glaucoma or ocular hypertension treated with either BAK-preserved latanoprost or BAK-free travoprost. Clin Ophthalmol 2010;4:1253-61.
102. Macky TA. Bimatoprost versus travoprost in an Egyptian population: a hospital-based prospective, randomized study. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics 2010;26:605-10.
103. Traverso CE, Ropo A, Papadia M, Uusitalo H. A phase II study on the duration and stability of the intraocular pressure-lowering effect and tolerability of Tafluprost

compared with latanoprost. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics 2010;26:97-104.
104. Whitson JT, Trattler WB, Matossian C, Williams J, Hollander DA. Ocular Surface Tolerability of Prostaglandin Analogs in Patients with Glaucoma or Ocular Hypertension. Journal of Ocular Pharmacology and Therapeutics 2010;26:287-92.
105. Nie X, Yang XH, Qin XF, Quan CJ, Yang SS. Correlation between the development of high myopia and intraocular pressure. International Journal of Ophthalmology 2011;11:1092-4.
106. Zhao L, Wang YL, Meng ZY, Hong H. Efficacy and safety of domestic Latanoprost in treating with open angle glaucoma and ocular hypertension. [Chinese]. International Journal of Ophthalmology 2011;11:1973-5.
107. Araie M, Yamazaki Y, Sugiyama K, Kuwayama Y, Tanihara H. Phase III clinical trial of brimonidine in patients with primary open-angle glaucoma and ocular hypertension--comparison of the effects of brimonidine monotherapy versus timolol monotherapy, or combination brimonidine/prostaglandins therapy versus combination placebo/prostaglandins therapy. Nippon Ganka Gakkai Zasshi - Acta Societatis Ophthalmologicae Japonicae 2012;116:955-66.
108. Chabi A, Varma R, Tsai JC, et al. Randomized clinical trial of the efficacy and safety of preservative-free tafluprost and timolol in patients with open-angle glaucoma or ocular hypertension. American journal of ophthalmology 2012;153:1187-96.
109. Crichton AC, Vold S, Williams JM, Hollander DA. Ocular surface tolerability of prostaglandin analogs and prostamides in patients with glaucoma or ocular hypertension. Advances in Therapy 2013;30:260-70.
110. Delval L, Baudouin C, Gabisson P, Alliot E, Vincent B. Safety and efficacy of unpreserved timolol 0.1% gel in patients controlled by preserved latanoprost with signs of ocular intolerance. Journal français d'ophtalmologie 2013;36:316-23.
111. Katz G, Dubiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. JAMA Ophthalmology 2013;131:724-30.
112. Nguyen QH, McMenemy MG, Realini T, Whitson JT, Goode SM. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. Journal of Ocular Pharmacology and Therapeutics 2013;29:290-7.
113. Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. Br J Ophthalmol 2015;99:738-45.
114. Chabi A, Baranak C, Lupinacci R, Herring WJ. Preservative-free tafluprost in the treatment of open-angle glaucoma or ocular hypertension in India: a phase III clinical trial. Int J Clin Pract 2016;70:577-86.

Appendix 3. Inconsistency analysis

Because the number of drugs included in different networks are different, we used the following codes to designate drugs in respective network:

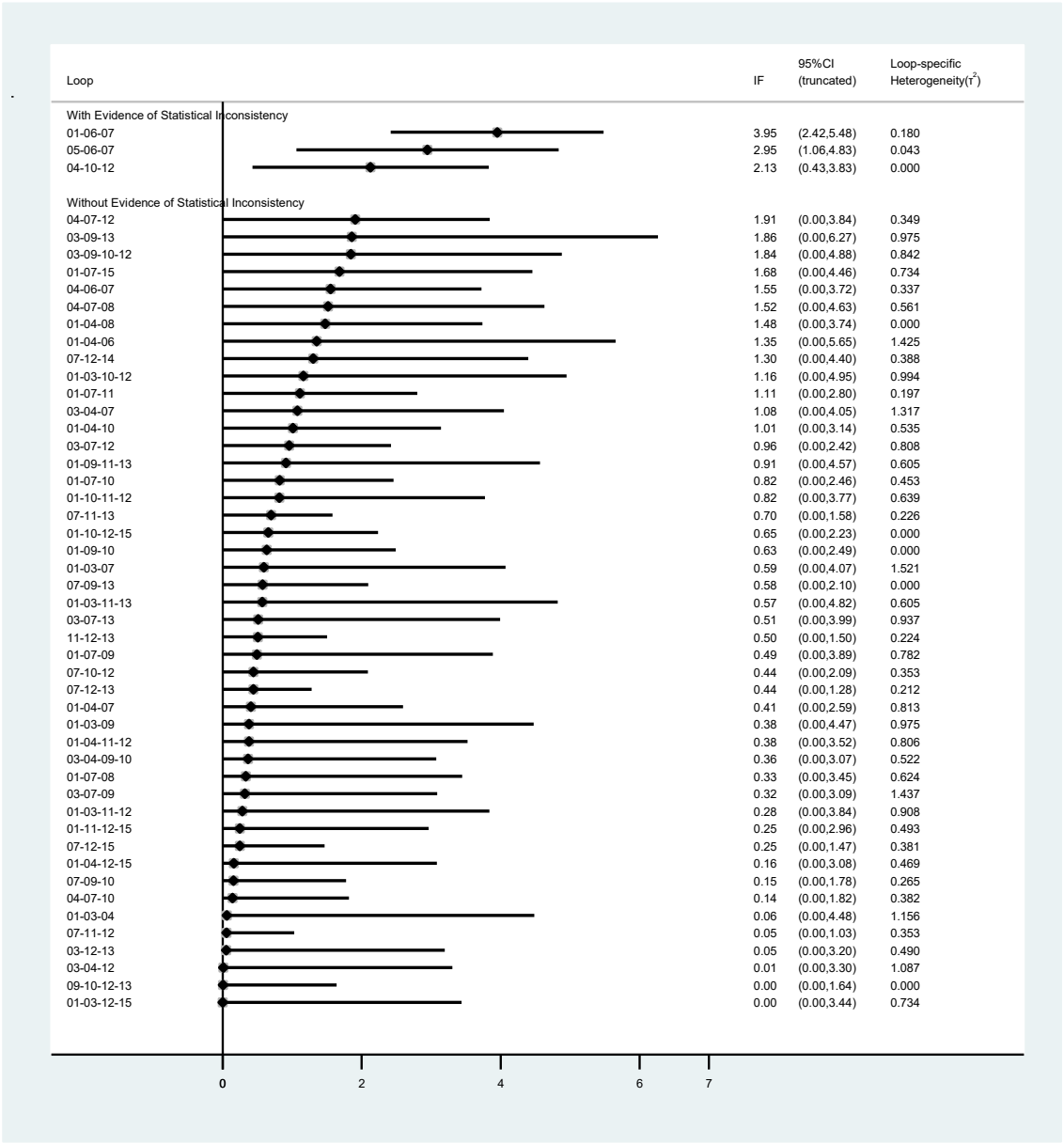
	Code			
Drug name	**All-unique trial**	**Published trial**	**FDA trial**	**CT.gov trial**
Placebo/Vehicle/No treatment	1	1	1	Not included
Apraclonidine	2	2	Not included	Not included
Brimonidine	3	3	Not included	1
Betaxolol	4	4	2	Not included
Carteolol	5	5	Not included	Not included
Levobunolol	6	6	Not included	Not included
Timolol	7	7	3	2
Levobetaxolol	8	Not included	4	Not included
Brinzolamide	9	8	5	3
Dorzolamide	10	9	6	Not included
Bimatoprost	11	10	7	4
Latanoprost	12	11	8	Not included
Travoprost	13	12	9	5
Tafluprost	14	13	Not included	6
Unoprostone	15	14	10	Not included

1. Loop-specific approach

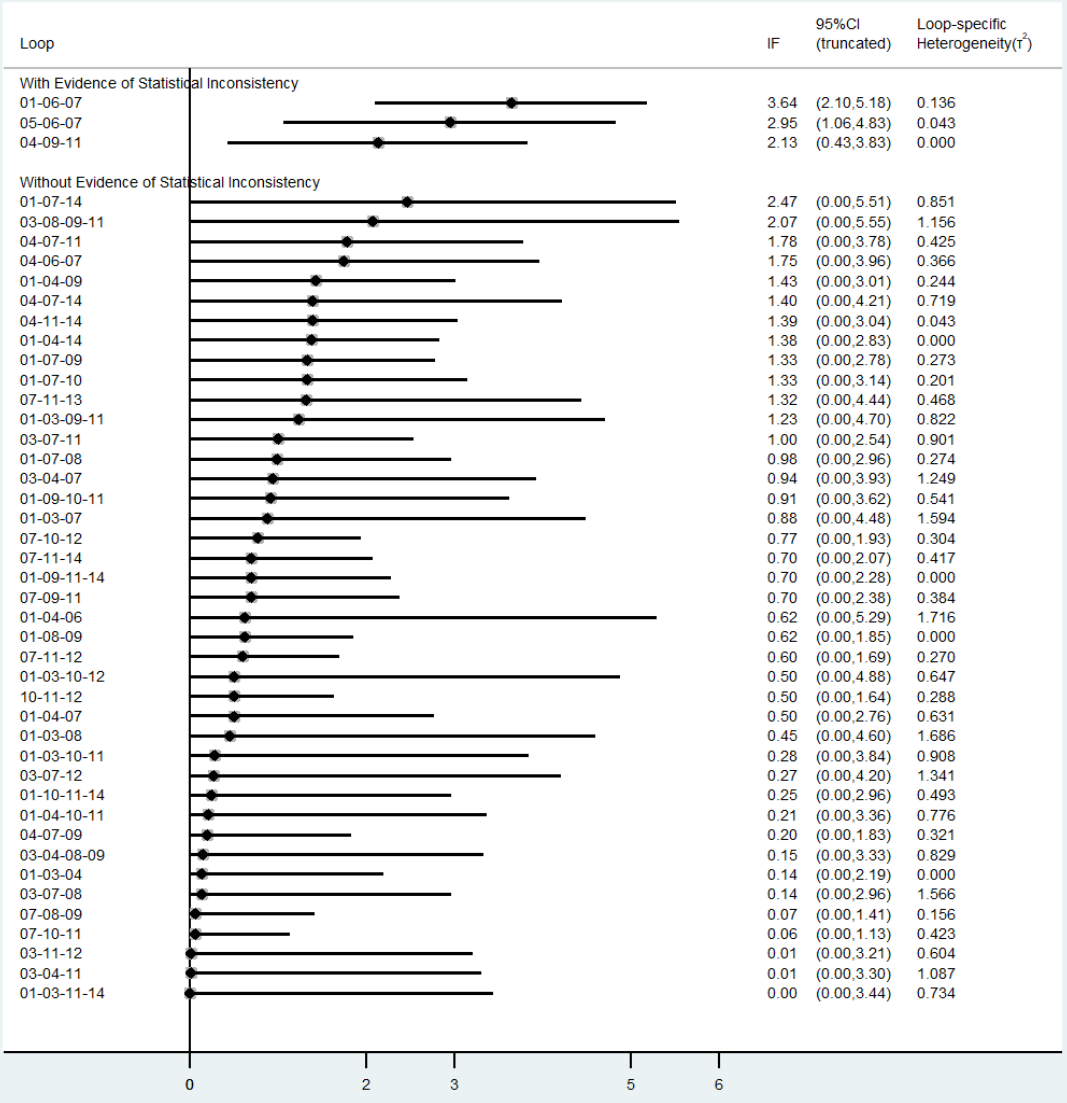
We used loop-specific approach to estimate an inconsistency factor (IF) for each closed loop in all-unique trial and published trial network. The IF is the difference between direct and indirect estimates. The following inconsistency plots (Appendix 3 figure 1 and 2) present all triangular and quadratic loops in the network and the respective IF and their 95% CIs. Statistically significant inconsistency is present when the lower CI of IF does not reach the zero line.

We detected evidence of statistical inconsistency in the three triangular loops of the all unique trial and in the same three triangular loops of published trial networks.

Appendix 3 Figure 1. Inconsistency plot (all-unique trial network)



Appendix 3 Figure 2. Inconsistency plot (published trial network)



2. Modeling inconsistency

We applied design-by-treatment interaction inconsistency models to check for overall inconsistency in each network. We found inconsistency at the overall level in the all-unique trial and the published trial networks (Appendix 3 table 1).

We compared the inconsistency model and consistency model using both AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion) for model fit. Inconsistency models did not improve the model fit (Appendix 3 table 2).

3. Side-split approach (Node-split approach)

We used side-specific approach to estimate local inconsistency in the all-unique trial and published trial networks. The following tables (Appendix 3 table 3 and 4) report the estimated direct and indirect effects and their differences. The p-value is a test of consistency. Evidence of statistical inconsistency was found in two sides of the all-unique trial network and the same two sides of the published trial network.

Appendix 3 Table 1 Modeling inconsistency testing results

Network	Chi-square	P value
All-unique trial	64.05	0.0038
Published trial	60.06	0.0072

Appendix 3 Table 2 Model-selection statistics

Network	Model	Number of trials	log likelihood	Degree of freedom	AIC	BIC
All-unique trial	Consistency	121	-773.2598	15	1576.52	1618.456
	Inconsistency	121	-709.0076	52	1522.015	1667.396
Published trial	Consistency	107	-678.8472	14	1385.694	1423.114
	Inconsistency	107	-615.5491	50	1331.098	1464.74

Legend: Akaike information criterion (AIC) and the Bayesian information criterion (BIC).

Appendix 3 Table 3. Side-split estimates (All-unique trial network)

	Direct		Indirect		Difference		
Side	Coefficient	SE	Coefficient	SE	Coefficient	SE	P value
01 03	-2.3	1.164134	-3.075347	0.3848194	0.7753472	1.226089	0.527
01 04	-2.254772	0.5559589	-2.28498	0.4439738	0.030208	0.7113948	0.966
01 06	**-7.443528**	**0.7374297**	**-3.647608**	**0.401637**	**-3.79592**	**0.8400829**	**<0.001**
01 07	-3.598537	0.4920707	-3.791175	0.3516375	0.192638	0.6044004	0.75
01 08	-2.690202	1.098351	-2.484202	0.6557017	-0.2059997	1.256402	0.87
01 09	-2.28	1.193074	-2.999094	0.4372812	0.7190939	1.270685	0.571
01 10	-1.597396	0.6407625	-2.626286	0.4127301	1.02889	0.7619672	0.177
01 11	-4.6	0.9320135	-5.760193	0.380059	1.160194	1.006526	0.249
01 15	-0.5	0.9882314	-2.137627	0.4466699	1.637627	1.084488	0.131
02 07*	-1.721988	0.8297689	-5.728755	141.4392	4.006767	141.4443	0.977
03 04	-0.0400334	0.931284	0.8651027	0.3969729	-0.9051361	1.012362	0.371
03 07	-0.758611	0.4602837	-0.7088643	0.3413367	-0.0497467	0.5725672	0.931
03 09	-0.3335984	0.4512047	0.6319677	0.5150939	-0.9655661	0.6847503	0.159
03 12	-1.13607	0.4117077	-2.201031	0.3744871	1.064961	0.5566703	0.056
03 13	-1.166894	1.51934	-1.941603	0.3482496	0.7747084	1.558254	0.619
04 06	-3.698475	0.9731842	-1.998906	0.4255329	-1.699569	1.062228	0.11
04 07	-1.746724	0.4076599	-1.159246	0.4073257	-0.5874778	0.575915	0.308
04 08	-1.943592	1.089464	0.311068	0.6455598	-2.25466	1.245588	0.07
04 10	-0.3469696	0.6533139	0.073912	0.4302213	-0.4208817	0.7822207	0.591
04 12	-1.045531	0.8808725	-2.655783	0.3442204	1.610252	0.9457974	0.089
05 06	-2.900099	1.155004	-0.6291871	0.5778235	-2.270912	1.29148	0.079
05 07	0.0631267	0.4910633	-2.208853	1.194386	2.27198	1.291373	0.079
06 07	**-0.0163721**	**0.3173688**	**3.324773**	**0.5555049**	**-3.341145**	**0.639411**	**<0.001**
07 08*	1.230483	0.5341989	0.7671107	1.548627	0.4633721	1.601289	0.772
07 09	0.8906295	0.7879835	0.7926974	0.3834832	0.0979322	0.8763087	0.911
07 10	1.20672	0.3992229	1.603108	0.4100332	-0.396388	0.5726677	0.489
07 11	-2.234394	0.357049	-1.564081	0.3267921	-0.6703128	0.4842143	0.166
07 12	-1.295281	0.2585126	-0.6589983	0.2696237	-0.636283	0.3741619	0.089
07 13	-0.9242972	0.3739428	-1.366098	0.324499	0.4418007	0.4948384	0.372
07 14	-0.9042284	0.6118585	-1.902382	1.509619	0.9981535	1.628926	0.54
07 15	1.43334	0.4914406	2.210808	0.4408102	-0.777468	0.6600149	0.239
09 10	0.3023935	0.6081101	0.7725025	0.4888086	-0.470109	0.7802174	0.547
09 13	-2.700056	1.023329	-1.86359	0.4282679	-0.8364654	1.109331	0.451
10 12	-2.900017	0.8840274	-2.312537	0.3437054	-0.5874803	0.9484925	0.536
11 12	0.9380867	0.3754434	0.8297019	0.3478069	0.1083848	0.51177	0.832
11 13	0.5237479	0.3143546	1.025894	0.4400789	-0.5021462	0.5408405	0.353
12 13	-0.053102	0.3558085	-0.3253227	0.3634745	0.2722206	0.5082481	0.592
12 14	-0.9003449	1.497957	0.0994905	0.6400987	-0.9998354	1.628979	0.539

	Direct		Indirect		Difference		
Side	Coefficient	SE	Coefficient	SE	Coefficient	SE	P value
12 15	2.930625	0.4469339	2.763982	0.4859581	0.1666432	0.6604505	0.801

Legend: *all the evidence about these contrasts comes from the trials which directly compare them.

Appendix 3 Table 4. Side-split estimates (Published trial network)

	Direct		Indirect		Difference		
Side	Coefficient	SE	Coefficient	SE	Coefficient	SE	P value
01 03	-2.3	1.187698	-3.144127	0.4074083	0.8441271	1.255631	0.501
01 04	-2.83293	0.6912884	-2.269799	0.4261333	-0.5631303	0.8120134	0.488
01 06	**-7.440595**	**0.7491729**	**-3.601976**	**0.4155754**	**-3.838619**	**0.8571359**	**<0.001**
01 07	-3.898235	0.5799344	-3.615408	0.3537606	-0.2828269	0.6791653	0.677
01 08	-1.809676	0.7810297	-2.925899	0.5312848	1.116223	0.9481578	0.239
01 09	-1.74374	0.5561203	-2.921061	0.4659918	1.177321	0.7253378	0.105
01 10	-4.6	0.9620217	-5.686724	0.4111015	1.086724	1.046179	0.299
01 14	-0.5	1.013886	-2.209539	0.4751332	1.709539	1.119695	0.127
02 07*	-1.709156	0.8496725	-5.67356	141.4329	3.964405	141.4383	0.978
03 04	-0.0400347	0.9619458	0.7537764	0.4123756	-0.7938111	1.046611	0.448
03 07	-0.7570194	0.4771192	-0.5629909	0.3712428	-0.1940285	0.6040083	0.748
03 08	-0.0077284	0.6455272	0.8347285	0.5469576	-0.8424569	0.846095	0.319
03 11	-1.127472	0.425508	-2.117483	0.4078233	0.9900111	0.5893447	0.093
03 12	-1.167744	1.537659	-1.753204	0.4012957	0.5854604	1.589331	0.713
04 06	-3.736638	0.9917545	-1.800841	0.433524	-1.935798	1.082356	0.074
04 07	-1.604731	0.4060524	-0.9020261	0.421495	-0.7027048	0.5856782	0.23
04 09	-0.3400322	0.674211	0.1354042	0.4540594	-0.4754365	0.8134583	0.559
04 11	-1.043914	0.8971274	-2.457442	0.3493604	1.413527	0.9628229	0.142
04 14	0.5956492	0.8629164	0.4967152	0.4958862	0.098934	0.9958656	0.921
05 06	-2.900098	1.177628	-0.6541258	0.5935108	-2.245972	1.318738	0.089
05 07	0.0649214	0.5048714	-2.18216	1.218171	2.247081	1.318626	0.088
06 07	**-0.0161534**	**0.3214898**	**3.420803**	**0.5624286**	**-3.436957**	**0.6474484**	**<0.001**
07 08	1.007501	0.6273221	1.193592	0.5116339	-0.1860917	0.8144236	0.819
07 09	0.9133038	0.435028	1.617772	0.4495557	-0.7044678	0.6273492	0.261
07 10	-2.160663	0.4045025	-1.559041	0.3631966	-0.6016216	0.5439324	0.269
07 11	-1.321821	0.2807638	-0.6619546	0.2926311	-0.6598662	0.4063371	0.104
07 12	-0.7041169	0.5317212	-1.253253	0.3617995	0.549136	0.6434583	0.393
07 13	-0.9106708	0.6342926	-1.919237	1.529757	1.008566	1.656074	0.543
07 14	0.949807	0.6177459	2.211388	0.4386942	-1.261581	0.7587647	0.096
08 09	-0.2512428	0.6607027	0.4374613	0.5847181	-0.6887041	0.8834773	0.436
09 11	-2.900018	0.9135118	-2.150094	0.3766852	-0.7499236	0.9881273	0.448
10 11	0.9389158	0.386214	0.7030374	0.3922596	0.2358784	0.550511	0.668
10 12	0.5875317	0.3388964	1.171842	0.5499201	-0.5843108	0.6457836	0.366
11 12	-0.0057505	0.4006879	-0.1568373	0.4392003	0.1510868	0.5943251	0.799
11 13	-0.900343	1.516195	0.10995	0.666295	-1.010293	1.65613	0.542
11 14	2.923878	0.4574624	2.605287	0.5499054	0.3185911	0.7157209	0.656

Legend: *all the evidence about these contrasts comes from the trials which directly compare them.

Appendix 4. Sensitivity analysis

For sensitivity analysis, we re-analyzed the all-unique trial network after removing 3 trials that are outliers and that may have resulted in heterogeneity and inconsistency. The effect estimates and ranking probabilities are consistent with primary analyses (Appendix 4 Table 1).

Appendix 4 Table 1. Summary estimates of mean difference in IOP at 3 months derived from NMA (all-unique trial network sensitivity analysis)

Bimatoprost	Travoprost	Tafluprost	Latanoprost	Levobunolol	Timolol	Carteolol	Brimonidine	Brinzolamide	Levobetaxolol	Dorzolamide	Betaxolol	Apraclonidine	Unoprostone	Placebo
-0.70 (-1.20,-0.19)	Travoprost	0.14 (-1.06,1.34)	0.18 (-0.32,0.68)	0.41 (-0.36,1.18)	1.19 (0.71,1.67)	1.46 (0.44,2.48)	1.90 (1.24,2.57)	1.98 (1.21,2.76)	2.37 (1.26,3.48)	2.57 (1.86,3.28)	2.66 (1.92,3.39)	2.91 (1.21,4.61)	3.03 (2.27,3.80)	4.84 (4.12,5.55)
-0.83 (-2.04,0.37)	-0.14 (-1.34,1.06)	Tafluprost	0.04 (-1.12,1.19)	0.27 (-1.00,1.54)	1.05 (-0.06,2.16)	1.32 (-0.11,2.75)	1.76 (0.53,2.99)	1.84 (0.55,3.14)	2.23 (0.73,3.73)	2.43 (1.19,3.67)	2.52 (1.26,3.77)	2.77 (0.80,4.74)	2.89 (1.62,4.17)	4.70 (3.45,5.95)
-0.87 (-1.37,-0.37)	-0.18 (-0.68,0.32)	-0.04 (-1.19,1.12)	Latanoprost	0.23 (-0.48,0.94)	1.01 (0.64,1.38)	1.28 (0.31,2.25)	1.72 (1.17,2.27)	1.81 (1.09,2.52)	2.19 (1.13,3.26)	2.39 (1.76,3.02)	2.48 (1.82,3.13)	2.73 (1.06,4.40)	2.86 (2.21,3.50)	4.66 (4.01,5.30)
-1.10 (-1.87,-0.34)	-0.41 (-1.18,0.36)	-0.27 (-1.54,1.00)	-0.23 (-0.94,0.48)	Levobunolol	0.78 (0.17,1.39)	1.05 (0.02,2.08)	1.49 (0.70,2.29)	1.58 (0.68,2.47)	1.96 (0.80,3.13)	2.16 (1.36,2.97)	2.25 (1.46,3.03)	2.50 (0.76,4.24)	2.63 (1.75,3.51)	4.43 (3.66,5.19)
-1.88 (-2.36,-1.41)	-1.19 (-1.67,-0.71)	-1.05 (-2.16,0.06)	-1.01 (-1.38,-0.64)	-0.78 (-1.39,-0.17)	Timolol	0.27 (-0.63,1.17)	0.71 (0.18,1.25)	0.80 (0.12,1.47)	1.18 (0.18,2.19)	1.38 (0.82,1.94)	1.47 (0.89,2.05)	1.72 (0.09,3.35)	1.85 (1.20,2.49)	3.65 (3.08,4.22)
-2.15 (-3.17,-1.14)	-1.46 (-2.48,-0.44)	-1.32 (-2.75,0.11)	-1.28 (-2.25,-0.31)	-1.05 (-2.08,-0.02)	-0.27 (-1.17,0.63)	Carteolol	0.44 (-0.60,1.49)	0.52 (-0.60,1.64)	0.91 (-0.44,2.26)	1.11 (0.06,2.17)	1.20 (0.13,2.26)	1.45 (-0.41,3.31)	1.57 (0.47,2.68)	3.38 (2.32,4.43)
-2.60 (-3.27,-1.93)	-1.90 (-2.57,-1.24)	-1.76 (-2.99,-0.53)	-1.72 (-2.27,-1.17)	-1.49 (-2.29,-0.70)	-0.71 (-1.25,-0.18)	-0.44 (-1.49,0.60)	Brimonidine	0.08 (-0.59,0.75)	0.47 (-0.66,1.60)	0.67 (-0.04,1.38)	0.75 (0.03,1.48)	1.01 (-0.70,2.72)	1.13 (0.34,1.93)	2.93 (2.21,3.66)
-2.68 (-3.47,-1.89)	-1.98 (-2.76,-1.21)	-1.84 (-3.14,-0.55)	-1.81 (-2.52,-1.09)	-1.58 (-2.47,-0.68)	-0.80 (-1.47,-0.12)	-0.52 (-1.64,0.60)	-0.08 (-0.75,0.59)	Brinzolamide	0.39 (-0.81,1.59)	0.59 (-0.16,1.33)	0.67 (-0.16,1.51)	0.93 (-0.84,2.69)	1.05 (0.15,1.96)	2.85 (2.04,3.66)
-3.07 (-4.18,-1.96)	-2.37 (-3.48,-1.26)	-2.23 (-3.73,-0.73)	-2.19 (-3.26,-1.13)	-1.96 (-3.13,-0.80)	-1.18 (-2.19,-0.18)	-0.91 (-2.26,0.44)	-0.47 (-1.60,0.66)	-0.39 (-1.59,0.81)	Levobetaxolol	0.20 (-0.94,1.34)	0.28 (-0.84,1.41)	0.54 (-1.38,2.45)	0.66 (-0.53,1.85)	2.46 (1.34,3.59)
-3.27 (-3.98,-2.56)	-2.57 (-3.28,-1.86)	-2.43 (-3.67,-1.19)	-2.39 (-3.02,-1.76)	-2.16 (-2.97,-1.36)	-1.38 (-1.94,-0.82)	-1.11 (-2.17,-0.06)	-0.67 (-1.38,0.04)	-0.59 (-1.33,0.16)	-0.20 (-1.34,0.94)	Dorzolamide	0.08 (-0.63,0.79)	0.34 (-1.38,2.06)	0.46 (-0.37,1.29)	2.26 (1.57,2.96)
-3.35 (-4.08,-2.62)	-2.66 (-3.39,-1.92)	-2.52 (-3.77,-1.26)	-2.48 (-3.13,-1.82)	-2.25 (-3.03,-1.46)	-1.47 (-2.05,-0.89)	-1.20 (-2.26,-0.13)	-0.75 (-1.48,-0.03)	-0.67 (-1.51,0.16)	-0.28 (-1.41,0.84)	-0.08 (-0.79,0.63)	Betaxolol	0.25 (-1.47,1.98)	0.38 (-0.47,1.22)	2.18 (1.49,2.87)
-3.60 (-5.30,-1.91)	-2.91 (-4.61,-1.21)	-2.77 (-4.74,-0.80)	-2.73 (-4.40,-1.06)	-2.50 (-4.24,-0.76)	-1.72 (-3.35,-0.09)	-1.45 (-3.31,0.41)	-1.01 (-2.72,0.70)	-0.93 (-2.69,0.84)	-0.54 (-2.45,1.38)	-0.34 (-2.06,1.38)	-0.25 (-1.98,1.47)	Apraclonidine	0.13 (-1.63,1.88)	1.93 (0.20,3.65)
-3.73 (-4.49,-2.97)	-3.03 (-3.80,-2.27)	-2.89 (-4.17,-1.62)	-2.86 (-3.50,-2.21)	-2.63 (-3.51,-1.75)	-1.85 (-2.49,-1.20)	-1.57 (-2.68,-0.47)	-1.13 (-1.93,-0.34)	-1.05 (-1.96,-0.15)	-0.66 (-1.85,0.53)	-0.46 (-1.29,0.37)	-0.38 (-1.22,0.47)	-0.13 (-1.88,1.63)	Unoprostone	1.80 (0.99,2.61)
-5.53 (-6.23,-4.83)	-4.84 (-5.55,-4.12)	-4.70 (-5.95,-3.45)	-4.66 (-5.30,-4.01)	-4.43 (-5.19,-3.66)	-3.65 (-4.22,-3.08)	-3.38 (-4.43,-2.32)	-2.93 (-3.66,-2.21)	-2.85 (-3.66,-2.04)	-2.46 (-3.59,-1.34)	-2.26 (-2.96,-1.57)	-2.18 (-2.87,-1.49)	-1.93 (-3.65,-0.20)	-1.80 (-2.61,-0.99)	Placebo

Legend:

1. Glaucoma drugs are expected to lower IOP; therefore, mean difference <0 favors the drug in the column, and mean difference >0 favors the drug in the row.
2. Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Appendix 4 Table 2. SUCRA values and mean ranks generated by NMA (all-unique trial network sensitivity analysis)

Drugs	SUCRA value	Mean rank
Bimatoprost	99.3	1.1
Travoprost	87.2	2.8
Tafluprost	82.9	3.4
Latanoprost	81.8	3.5
Levobunolol	76.5	4.3
Timolol	62.2	6.3
Carteolol	55.4	7.2
Brimonidine	46	8.6
Brinzolamide	43.3	8.9
Levobetaxolol	31.9	10.5
Dorzolamide	25.3	11.5
Betaxolol	23.3	11.7
Apraclonidine	20.9	12.1
Unoprostone	13.9	13.1
Placebo	0.1	15

Legend:
Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

Curriculum Vitae

Lin Wang
443-333-0261 • linwang@jhu.edu

PROFILE

Master of Science(ScM) student in Epidemiology with concentration on clinical trial and evidence synthesis and additional training in health finance, pharmacoepidemiology and drug safety. Medical doctor, former China FDA employee, and public health professional with strong program management and of resource implication skills. Fluent in Chinese and English.

EDUCATION

Master of Science(ScM) in Epidemiology, GPA 3.97/4.0 Expected May 2018
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Concentration: Clinical Trial and Evidence Synthesis
Graduate Certificate in Pharmacoepidemiology and Drug Safety May 2017
Graduate Certificate in Health Finance and Management Expected May 2018
Graduate Certificate in Clinical Trials Expected May 2018
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Master of Clinical Medicine（Dermatology and Venereology） June 2007
Central South University, China
Bachelor of Medicine (Equivalent to Doctor of Medicine in US) June 2004
Central South University, China

RESEARCH AND TEACHING EXPERIENCE

Research Assistant
Department of Epidemiology, Johns Hopkins School of Public health 2016-2018
First author of a NIH funded network meta-analysis project ranking the first-line glaucoma medications with information from bibliographic databases, FDA, and from ClinicalTrials.gov.
Reviewer for *Trials* journal.

Research Assistant
Department of Medicine, Johns Hopkins Hospital 2017-2018
Second author of three Johns Hopkins Hospital systematic review and meta-analysis projects on Non-alcoholic Fatty Liver Disease, Irritable Bowel Syndrome, and obesity respectively.

Teaching Assistant
Department of Epidemiology, Johns Hopkins School of Public health 2016-2018
Courses: Introduction to Clinical Trial, Systematic Review and Meta-Analysis, Clinical Trials: Procedures, Design, and Interpretation of Results

Principal Investigator

Xiangya hospital of Central South University, Changsha, China 2004-2007
First author of two clinical researches on Seborrhoeic Dermatitis and Postadolescent Acne respectively.

WORK EXPERIENCE

Principal Staff Member
China Food and Drug Administration, Peking, China 2012-2016

- Formulated and implemented policies, procedures and technical requirements concerning clinical trials and drug approval.
- Key member of working group on the revision of China Drug Administration Law.
- Organized training programs and inspection cooperation with US FDA, European Medicines Agency, and World Health Organization.
- Key member of an international working group on the formulation of General Principle on Designing Multi-Regional Clinical Trials(E17) at International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Senior Staff Member
Health Department of Guangdong Province, Guangzhou, China 2009-2012

- Headed a HIV/AIDS free diagnosis and antiretroviral treatment project with a 10,000-patient population and hundred million RMB yearly government budget.
- Managed a blindness prevention project that healed more than 2000 cataract patients.
- Organized medical support for 2010 Asian Olympic Games in Guangzhou.

Physician
Shenzhen Port Hospital, China 2007-2009

- Internal medicine for international patients. Received 6 months' training of Emergency Medicine and ICU in Peking University Shenzhen Hospital.

PROFESSIONAL DEVELOPMENT

Language Skills: Fluent Chinese and English
Computer Skills: Proficient in Word, Excel, PowerPoint, Access, SQL, REDCap, STATA, R, and SAS.
Training (on site): Network meta-analysis at Columbia University (2017), Statistics and Analysis of Data in Switzerland (2013), Mass Casualty Management in WHO (2010)

PUBLICATIONS

Published:
1. **Lin Wang** et al. Relationship of acne with chronic stress and androgen levels in postadolescent women. Chinese Journal of Dermatology. March 2008, Vol.41, No.3
2. **Lin Wang** et al. 0.1% Tacrolimus Ointment treatment for 60 seborrhoeic dermatitis patients. Chinese Journal of Dermatology September 2007, Vol. 40, No.9
3. George Kunnackal John, **Lin Wang**, Julie Nanavati1, Rajdeep Singh, Gerard Mullin Dietary alteration of the gut microbiome and its impact on weight and fat mass: A systematic review and meta-analysis. Genes 2018, 9(3), 167

4. Behnam Saberi, Alia S Dadabhai, Julie Nanavati, **Lin Wang**, Russell T Shinohara, Gerard E Mullin Vitamin D levels do not predict the stage of hepatic fibrosis in patients with non-alcoholic fatty liver disease: A PRISMA compliant systematic review and meta-analysis of pooled data World J Hepatol. Jan 27, 2018; 10(1): 142-1

Publishable Manuscript (ScM thesis): Accelerating network meta-analysis production with FDA approval packages and ClinicalTrials.gov- a case study on first-line medications for glaucoma